

AD-A206 082



DEALING WITH UNCERTAINTY IN

CHEMICAL RISK ANALYSIS

THESIS

David S. Clement
Captain, USAF

AFIT/GOR/MA/88D-2

DTIC
ELECTE
29 MAR 1989

DEPARTMENT OF THE AIR FORCE
AIR UNIVERSITY

AIR FORCE INSTITUTE OF TECHNOLOGY

Wright-Patterson Air Force Base, Ohio

This document has been approved
for public release and sale; its
distribution is unlimited.

89 3 29 047

AFIT/GOR/MA/88D-2

DEALING WITH UNCERTAINTY IN
CHEMICAL RISK ANALYSIS
THESIS

David S. Clement
Captain, USAF

AFIT/GOR/MA/88D-2

DTIC
ELECTE
S 29 MAR 1989 D
E

Approved for public release; distribution unlimited

DEALING WITH UNCERTAINTY IN CHEMICAL RISK ANALYSIS

THESIS

Presented to the Faculty of the School of Engineering
of the Air Force Institute of Technology
Air University
In Partial Fulfillment of the
Requirements for the Degree of
Master of Science in Operations Research

David S. Clement, B.S.
Captain, USAF

December 1988

Accession For	
NTIS GRA&I	<input checked="checked" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	
By _____	
Distribution/	
Availability Codes	
Dist	Avail and/or Special
A-1	

Approved for public release; distribution unlimited



Preface

This thesis incorporates the various methods for obtaining the unit risk number of a chemical into one unified process. I was not familiar with the chemical risk assessment process prior to working on this thesis. My interest in doing research on the chemical risk process was mainly founded out of curiosity. I realized the decisions associated with hazardous waste are enormous and if I, as an outsider, could shed a little light on just a small piece (unit risk) then maybe the enormity of the task could be reduced.

I would like to thank the people who without them I would surely have failed. First, I thank my adviser, Captain Joseph A. Tatman, who suggested that I could do this work, but insisted that it would not be easy. Joe was there to keep me in line and always had positive words of encouragement. Also, I thank my sponsors, Lt. Colonel Clewell and Dr. Melvin Andersen, who said they were never too busy for my confused questions. I was in their office every week picking their brains, and never would have understood the chemical risk assessment process without their help. In addition, I thank my reader, Dr. James W. Chrissis, for the constructive comments which have made this thesis more palatable. And finally, I thank my wife Judy, daughter Theresa, and son Paul, who have supported me through this entire ordeal. How did we ever find the time to have a baby son?

Lastly, I wish other AFIT students will be as fortunate as I.

David S. Clement

Table of Contents

	Page
Preface	ii
List of Figures	v
List of Tables	vi
Abstract	vii
I. Introduction	1
Specific Problem	1
Key Terms	1
Carcinogen	1
Unit Risk Number	1
Pharmacokinetics	2
General Background	3
Risk Assessment Process	3
Statistical Methods	4
PBPK Methods	5
Problem Statement	6
Scope	6
Methodology	7
II. Model Development	8
Flowchart	8
Bioassay	8
Species Internal Dose	10
Risk-per-Dose	10
Human Internal Dose	11
Target Dose	11
Unit Risk Number	12
Tree Diagram	12
Dioxin Tree	14
DCM Tree	15
DCM PBPK Tree	19
Assumptions	19
Model Summary	20
III. Combining Expert Opinion	21
The Problem	21
Combining Techniques	21
Mathematical Approach	22
Arithmetic Average	22
Geometric Average	22
Ranked or Weighted Average	22

Combining Expert Opinion Cont'd

	Bayesian	23
	Pseudo-Bayesian	23
	Interaction Approach	23
	Delphi Method	24
	Face-to-Face	25
	Discussion	26
	Categories	26
	Conditional Independence	26
	Sensitivity Analysis	28
	Choosing the Experts	28
	Recommended Procedure	28
IV.	DCM Unit Risk Analysis	30
	Assigning Preference Weights	30
	PBPK Variable Analysis	32
	PBPK Variable Values	32
	PBPK Sensitivity Analysis	32
	Weighted Average of Unit Risk	35
	Unit Risk Distribution	37
	Stochastic Sensitivity	39
	Discussion	41
V.	Dioxin Risk-Specific Dose	42
	Assigning Preference Weights	42
	Weighted Average of Risk-Specific Dose	42
	Discussion	44
VI.	Summary, Conclusions and Recommendations	45
	Summary	45
	Conclusions	45
	Recommendations	46
Appendix A:	The Physiologically-Based Pharmacokinetic Model for Methylene Chloride	47
Appendix B:	Linear Multi-Stage Dose Response Model	55
Appendix C:	Calculating DCM Unit Risk Numbers	57
Bibliography	62
Vita	65

List of Figures

Figure	Page
1. Chemical Risk Assessment Flowchart	9
2. Dioxin Tree Diagram	16
3. Methylene Chloride (DCM) Tree Diagram	17
4. PBPK Variable Tree Diagram for Human and Animal	18
5. PBPK Stochastic Sensitivity Analysis	34
6. Reduced Methylene Chloride Tree Diagram . . .	36
7. Unit Risk Distribution for DCM	38
8. DCM Unit Risk Sensitivity Analysis	40
9. Dioxin Tree Diagram w/ Preference Weights .	43

List of Tables

Table	Page
1. DCM Preference Weights given by Andersen . .	31
2. DCM Preference Weights for PBPK Tree	31
3. PBPK Variables' Range	32
4. Stochastic Sensitivity of the PBPK Variables	35
5. Unit Risk Numbers for the DCM Tree	37
6. Stochastic Sensitivity of the DCM Tree Assumptions	39

Abstract

For a given chemical there are usually several methods for estimating the risk. Each method is based on different assumptions. The arguments are plentiful for each method, but which method best estimates the risk? Choosing one method over another could lead to faulty risk estimates, thus the traditional methods have been very conservative to avoid underestimating the risk. With advances made in pharmacokinetics the EPA as come under pressure to re-evaluate its procedure for assigning risk. Which method or methods should be used and how much emphasis should be placed on each one? This study decomposes the various methods into their corresponding assumptions. A tree diagram is generated to describe the combinations of assumptions that make up each unit risk method. A subjective weight is assigned to each assumption (branch of the tree) to characterize its validity in estimating the risk. From this a weighted average of risk is calculated. A procedure is recommended for combining expert opinion when several experts are utilized in assigning the subjective weights. Two examples involving Methylene Chloride and 2,3,7,8-tetrachlorodibenzo-p-dioxin illustrate the decomposition method of estimating chemical risk.

DEALING WITH UNCERTAINTY IN CHEMICAL RISK ANALYSIS

I. Introduction

Specific Problem

A basic problem facing the U.S. Environmental Protection Agency (EPA) is what method to use in determining the unit risk number of a chemical that have shown to be carcinogenic. Traditionally, experimental animal studies and particular statistical methods have been used in determining the unit risk number. Recently, physiologically based pharmacokinetic models (PBPK) "have been developed for a variety of volatile and nonvolatile chemicals, and their ability to perform the extrapolations needed in risk assessment has been demonstrated" (Clewell and Andersen, 1985:111). This study develops an analytical method that allows for several models, including PBPK models, to be incorporated into the risk assessment process.

Key Terms

Carcinogen. A carcinogen is any substance that is associated with producing cancer:

Cancer is now considered to be the end result of a multistage process in which a large number of endogenous and exogenous factors interact, simultaneously or in sequence, to disrupt normal cell growth and division [Wilkinson, 1987:844].

Unit Risk Number. "Risk assessment is the necessary process of determining human health risks from exposure to chemicals" (Menzel, 1987:944). The unit risk number of a chemical is the probability of a

person developing cancer if exposed to a set concentration of the chemical in the air breathed or in the food and water that is ingested.

A chemical may have several unit risk numbers:

1) A unit risk number associated with continuous inhalation of a specific exposure concentration such as $1\text{ug}/\text{m}^3$.

2) A unit risk number associated with an occupational exposure such as being exposed to 1 part per million (ppm), 8 hours per day, 5 days per week, and 48 weeks per year.

3) Or a unit risk number associated with ingesting the chemical, such as when drinking contaminated ground-water. The unit risk number would then be a risk per 1 mg/liter.

For example: suppose the unit risk number of methylene chloride (DCM), an important solvent used in paint removers, is 4.7×10^{-7} for continuous inhalation of 1 microgram of DCM per cubic meter of air per day ($1\text{ug}/\text{m}^3$, or $1 \times 10^{-6}\text{g}/\text{m}^3$). Then a person breathing 1 ug of methylene chloride per cubic meter of air each day over his life time would have a 4.7×10^{-7} chance of developing cancer. Likewise, the higher the concentration the higher the probability. The unit risk number is usually given as the probability of developing cancer from continuous exposure to 1 ppm, 1 mg/kg/day, or 1 pg/kg/day of chemical.

Pharmacokinetics. Pharmacokinetics is "the quantitative study of the metabolic processes of absorption, distribution, biotransformation, and elimination" (Calabrese, 1987:619). Physiologically-based pharmacokinetic models (PBPK) are defined as follows:

They are essentially mechanistic models that try to account quantitatively over time for the various pharmacokinetic processes that involve an agent [chemical] of concern from the time the agent reaches a site of absorption to the time an interaction occurs between the agent, its metabolites, and various body tissues [Calabrese, 1987:620].

PBPK models are designed to determine the relationship between the

internal dose in the tissues and the amount of applied dose (EPA, July 1987:47).

General Background

The Risk Assessment Process. The EPA is responsible for assigning unit risk numbers to chemicals that have been shown to be carcinogenic. A chemical is considered carcinogenic if it has been found to promote cancer in animals during long-term experiments (EPA, September 1986:33995). Usually, the EPA contracts with a lab to test a chemical that is suspected to be carcinogenic as defined by EPA Guidelines for Carcinogen Risk Assessment (EPA, September 1986). The EPA then evaluates the laboratory studies ...

according to sound biological and statistical considerations and procedures. Results and conclusions concerning the agent [chemical] derived from different types of information ... are melded together into a weight-of-evidence determination. The strength of evidence supporting a potential human carcinogenicity judgment is developed in a weight-of-evidence stratification scheme [EPA, September 1986:33994] ...

which is used in assigning a unit risk number to the chemical. The EPA uses more than the laboratory results in determining the unit risk number. The EPA asks for comments from the scientific community. Both industrial and environmental groups present arguments for lowering or raising the unit risk number. Based on the experimental findings and community debate, the EPA then publishes a unit risk number for the chemical.

The Armstrong Aerospace Medical Research Laboratory, Toxic Hazards Division, is responsible for advising on the toxicity of AF chemicals and has provided input to the EPA on issues relating to AF use of toxic chemicals. The AF is tasked with cleaning up their hazardous waste

sites, and spends approximately 500 million dollars a year on cleaning up their hazardous waste sites. The unit risk number dictates the cleanliness standard the AF must meet. A high probability unit risk number means tougher exposure standards, and tougher standards make for higher clean up costs, and the higher costs add up to fewer hazardous waste sites getting cleaned. With increasing public support for cleaning all hazardous waste sites, the AF is driven to use its limited budget for cleaning up as many hazardous waste sites as possible. If the unit risk number is unreasonably conservative the budget is wasted on over cleaning. But if the unit risk is set too low, people are exposed to a greater risk than is publicly acceptable. Again society bears the cost of the medical expenses in treating the exposed individuals. Of course nobody wants an unsafe environment, but wasting precious resources (budget) on over stringent clean up standards is poor policy. Good science should lead to sound policy that all of society can live with.

Statistical Methods. The traditional method of assessing risk, as stated earlier, starts with long-term animal exposure studies. During these tests, animals (usually mice) are exposed to various high concentrations of the chemical in their air, or water, or feed. If the animals develop tumors, then the chemical is classified as a probable human carcinogen. The probability of the animals developing cancer from various exposure doses is determined and is used for extrapolating the probability of developing cancer in humans.

The statistical methods for determining unit risk numbers have been improved over the years, but they still rely on extrapolating the risk

in animals to the risk in humans. The methods have assumed humans to be more sensitive to the tested chemical than the lab animals (body surface method). This may not always be true (Calabrese, 1987:620). Some methods, when extrapolating from high dose to low dose (dose response models), ignore the possibility that below a certain threshold level the chemical may pose no risk of cancer at all. In addition, bioassays are performed exposing the animal to contaminated air and water, for which the concentrations are known (external factors), and the internal tissue concentrations of the chemical are based on these external concentrations and the animal's breathing rate. The chemical is assumed to be completely absorbed into the animal's body, which completely neglects the physiological aspects of the body in dealing with the chemical (Menzel, 1987:944). Every year more and more research is done that adds to our understanding of human and animal physiology. The EPA wants to take advantage of this information when assigning unit risk numbers.

PBPK Methods. During the past few years, there have been great strides made in understanding the physiological basis of how mammals process chemicals in the blood stream.

By using physiologically based mathematical models of the transport, distribution, and metabolism of toxic chemicals, scientists can predict and confirm the organ or intracellular dose of the chemical by experimental analysis in exposed animals. By this process the exposure concentration is converted to a tissue dose [Menzel, 1987:945].

As with most new methods, these PBPK approaches have yet to gain widespread acceptance. The advantage of PBPK models over existing statistical methods is that PBPK models are "based to a large extent on the actual physiology of the organism [Clewett and Andersen, 1985:114]."

"Since the relationship between the effective dose [internal dose, target dose, or surrogate dose] and the administered dose [external dose] may be nonlinear, pharmacokinetic considerations can significantly modify low-dose risk estimates regardless of the model employed [Federal Register, 1985:81]." PBPK models have provided a better understanding of the way the body processes chemicals, but as yet have only been marginally used in risk assessment (Andersen and Clewell, 1988).

The EPA is interested in using new approaches for assigning the unit risk number (Shabecoff, 1988). The PBPK models can provide more realistic data on the effects chemicals have on the body. Four alternatives have been suggested where PBPK models may aid the EPA in assigning the unit risk number (Cohn, 1987:2):

- 1) PBPK models are ignored (too new and not proven).
- 2) PBPK models could assist in extrapolating from the high to low dose.
- 3) They could assist in the species-to-species extrapolation.
- 4) PBPK models could be used in both dose and species extrapolations.

Problem Statement

The EPA is interested in improving the way the unit risk numbers are determined for carcinogens. What is needed is a method that addresses the uncertainties associated with the various techniques for assigning chemical risk and to combine them, including the PBPK modeling technique, into one cohesive unit risk assessment process.

Scope. This study will develop a methodology for assigning unit risk numbers by combining both the traditional methods and the PBPK modeling techniques into one risk assessment process, with emphasis on methodology for assigning the unit risk number and not on the unit risk

number itself. The study is limited to two chemicals: methylene chloride (DCM) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin). Both chemicals are used for illustrating the method.

Methodology. Several methods can be evaluated for determining the risk of a chemical by decomposing them into their corresponding assumptions. A subjective probability is then assigned to each assumption to characterize its validity in estimating the risk. From this a weighted average of risk is calculated.

A general discussion of dealing with uncertainty of the assumptions using tree diagrams is presented first. Then how to combine experts' subjective weights is reviewed. And finally two examples involving DCM, an important industrial solvent used by the AF for paint striping operations, and dioxin will illustrate the process. DCM shows how to incorporate pharmacokinetics into the risk assessment process since it is one of the few chemicals to have a good PBPK model built for it. And dioxin was chosen to show the flexibility of the decomposition process because the risk associated with it was developed differently than DCM.

II. Model Development

There are a variety of ways for determining the risk of a carcinogen. Chapter I discussed the overall process. Here the process will be examined in a flowchart like fashion. Hogarth (1986:146) suggests "decomposing the problem into appropriate components", thus it becomes easier to understand.

Flowchart

The unit risk number assessment flowchart is shown in Figure 1. Each sequence in the flowchart is as follows:

Bioassay. The first step in assessing the unit risk number for any suspected carcinogen is to conduct a bioassay to determine the effect it has upon animals. The bioassays are laboratory experiments carried out on animals, usually rats or mice, in the expectation of determining the risk (probability of developing cancer, or some other measured effect) associated with exposure to the suspected carcinogen. The risk associated with the bioassay is dependent on several factors:

- 1) *Suspected Carcinogen*, (in this case dioxin and DCM).
- 2) *Dose*, the concentration administered to the animal.
- 3) *Route*, exposure via air, water, food, or touch.
- 4) *Effect*, does the suspected carcinogen cause cancer, tumors, disrupt the immune system or reproductive track, alter cell growth, or maybe create nervous system disorders?
- 5) *Species*, several different species could be used, but some animals do not react the same way as a human would if exposed to the same chemical. Depending on what effect is expected a specific animal is used.

The administered dose is usually very high in order to promote the

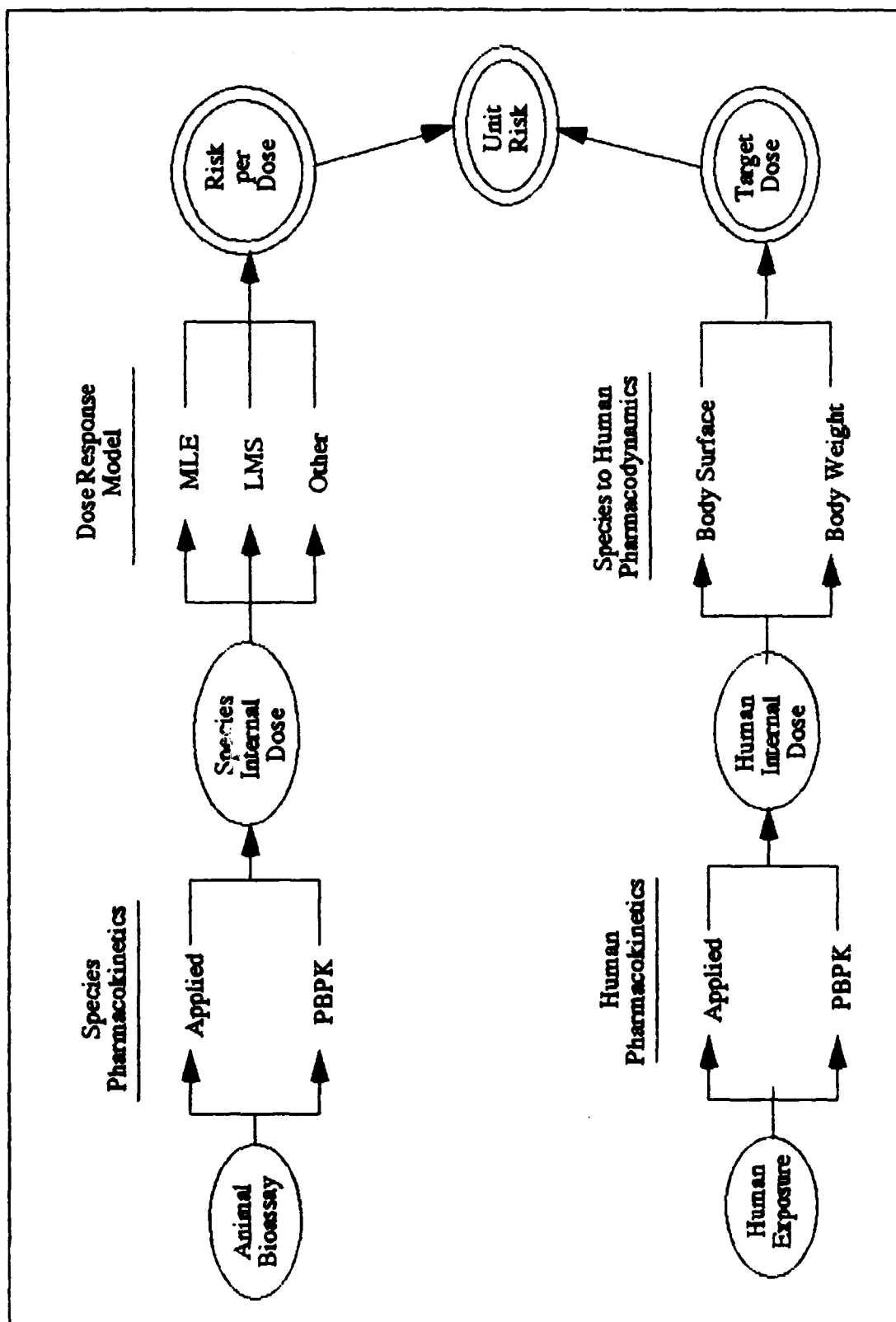


Figure 1. Chemical Risk Assessment Flowchart.

development of the effect in the animal. If the dose is too small, the effect may not develop prior to the animal dying a natural death. Once the bioassay is complete, it can be used in several ways to extrapolate the risk from animal to human.

Species Internal Dose. The species' internal dose is calculated in one of two ways: using the applied dose technique or the PBPK model.

1) Applied dose technique. The animal's administered dose (ppm) is converted to an internal dose. The administered dose is multiplied by the animal's breathing rate and divided by its body weight to obtain an internal dose in units of mg/kg/day. For example, if a mouse is exposed to 4000 ppm of DCM for 6 hours a day, 5 days a week, then the average daily internal dose is:

$$\begin{aligned}\text{int. dose} &= (4000 \text{ ppm}) * (3.4766 \text{ m}^3/\text{m}^3/1 \text{ ppm}) \\ &\quad * (0.043 \text{ m}^3/\text{day}) * (1/0.0345 \text{ kg}) \\ &\quad * (6 \text{ hrs}/24 \text{ hrs}) * (5 \text{ days}/7 \text{ days})\end{aligned}$$

$$\text{int. dose} = 3095 \text{ mg/kg/day}$$

2) PBPK model technique. This time the administered dose is converted to an internal dose (tissue dose or dose surrogate) using a physiologically-based pharmacokinetic (PBPK) model (Andersen et al, 1987). Refer to appendix A for details on the PBPK model.

Risk-per-Dose. The risk-per-dose is obtained by taking the bioassay results and the species internal dose and plugging them into a dose response model. One of these dose response models is the linear multistage (LMS) model which provides a 95 percent lower confidence limit (LCL) on dose. The LMS model has been commonly used by the EPA since it provides a conservative upper confidence limit on risk (Munro and Krewski, 1981:553; EPA, November 1987:27-31). Another method uses the maximum likelihood estimator (MLE) for dose instead of the 95 percent LCL. Traditionally, the dose response risk has been obtained using safety factors. The risk associated with the bioassay is

multiplied by some safety factor (e.g., 100 - 1000) to obtain the risk for a given dose (EPA, November 1987:34). For example, using the LMS model the number of animals which developed cancer for the given sample size and exposure rate is extrapolated to a 95 percent lower confidence limit dose for a 1×10^{-8} chance of cancer. Refer to appendix B for details on the LMS dose response model.

Human Internal Dose. The human internal dose is calculated much the same way as the species internal dose, but this time the human exposure dose is set to some standard setting, such as a continuous exposure to 1 ug/m^3 . The human internal dose is calculated in one of two ways: using the applied dose technique or the PBPK model.

1) Applied dose technique. The exposure of interest is then converted to an internal human dose as follows:

$$\text{int. dose} = (1 \text{ ug/m}^3) * (.001 \text{ mg/1 ug}) * (20 \text{ m}^3/\text{day}) * (1/70 \text{ kg})$$

$$\text{int. dose} = 0.000286 \text{ mg/kg/day}$$

2) PBPK model technique. In this case the dose of interest is converted using the physiologically-based pharmacokinetic (PBPK) model (Andersen et al, 1987).

Target Dose. The human internal dose is multiplied by the species-to-human pharmacodynamics correction factor to get the tissue target dose. There are two correction factors:

1) Body weight (BW). Since the internal dose is already in units of weight (kg) the BW correction factor is 1.

2) Body surface (BS). When using the body surface factor a human is considered more sensitive to the chemical exposure than the animal. The internal dose calculated above is multiplied by the body surface ratio to obtain a larger internal dose. The body surface ratio is the human's weight to animal's weight raised to the 1/3rd power. For a mouse the BS correction factor is:

$$\text{BS} = (70 \text{ kg}/0.0345 \text{ kg})^{1/3}$$

$$\text{BS} = 12.66$$

Thus, the body surface internal dose is approximately 12.7 times larger and will make the unit risk number of a chemical 12.7 times higher than if calculated using the body weight method.

Unit Risk Number. After obtaining the animal's risk-per-dose factor and human target dose, the unit risk number for a given exposure can be determined. For example:

$$\text{Unit Risk} = \text{risk-per-dose} * \text{target dose}$$

$$\text{Unit Risk} = \frac{1 \times 10^{-8}}{1.3 \times 10^{-5} \text{ mg/kg/day}} * 2.8 \times 10^{-4} \text{ mg/kg/day}$$

$$\text{Unit Risk} = 2.15 \times 10^{-7} \text{ for a continuous exposure to } 1 \text{ ug/kg/day of chemical}$$

The unit risk number could either be the probability of developing the effect at some set dose, as in the above example, or it could be the maximum recommended dose (risk-specific dose) at a set probability (e.g., 10^{-4} , 10^{-5} , or 10^{-6}), as is the case for dioxin.

Tree Diagram

There has been much controversy on the appropriate method for determining the unit risk number of a chemical. Any policy put forth that suggests a specific unit risk number for a particular chemical is usually criticized for some of its assumptions. There is always someone who disagrees on how the assumptions were made or what techniques were utilized. In a majority of cases the unit risk number is developed using a combination of the most likely, and sometimes most conservative, assumptions for a given chemical and effect. The problem with this approach is that other assumptions, even though less likely, are not considered in the final unit risk.

If all potential assumptions could be weighted according to their likelihood of estimating the unit risk number, then a weighted average

of the unit risk numbers could be determined. In other words, by taking the various methods for determining the unit risk number and weighting each according to the assumptions used, then a weighted average unit risk number can be calculated, where the weights reflect the decision makers belief in each assumption's ability to accurately determine the unit risk. The assignment of the unit risk number could then take on the form of a tree diagram with the branches representing each potential assumption; at the end of the branches would be the unit risk numbers for the various combinations of assumptions. Weights would be assigned by the decision maker (EPA) to each branch for the likelihood of that branch in estimating the unit risk number. Thus, all arguable combinations of assumptions could be considered in obtaining the unit risk.

The weights fall into two classes: preference weights and likelihood weights. The weights associated with the species pharmacokinetics, human pharmacokinetics, and pharmacodynamics reflect the decision makers belief (preference) of how well the branch predicts the unit risk of a chemical. The values of the PBPK variables and their respective probabilities (likelihood weights) reflect the likelihood of the actual or true value of the variable (a percentile of the variable's probability distribution on value). Mixing the preference weights with likelihood weights has no theoretical basis, so the decomposition method splits the tree diagram into two areas: preference weights and likelihood weights (probabilities). The likelihood weights associated with the PBPK variables are grouped into one tree and an expected value of unit risk is calculated. Then, the expected value of unit risk is

inserted in the preference weight tree and a weighted average of unit risk is determined.

There are two major drawbacks in using every tree combination for assigning the unit risk number: 1) there is not enough time or money to study every potential combination, and 2) how to get a consensus on what weight to assign each branch. Obtaining consensus for the weights will be discussed in the next chapter, and by only developing a tree based on current information will the need to study every potential combination be eliminated. As more information is learned on a specific chemical the tree may have to be enlarged to accommodate this new information. New weights would be assigned to both new and existing branches and another weighted average unit risk number calculated. Hence, the tree diagram would be the framework for analyzing the unit risk of a chemical. Dioxin and DCM are used to illustrate building trees for calculating chemical risk.

Dioxin Tree. The information used for developing a dioxin tree came from "A Cancer Risk-Specific Dose Estimate For 2,3,7,8-TCDD" from the EPA (EPA, November 1987). This report contains a summary of acceptable studies (14 in all) for generating a risk-specific dose for dioxin, which is the acceptable dose for a unit risk number of 1×10^{-6} . The studies were grouped according to assumption in developing a tree diagram. Four studies used the traditional safety factor approach, sometimes referred to as the no effect level (NOEL) approach, meaning that below some threshold value the risk is assumed to be zero. The remaining ten studies assumed no threshold and thus there is a chance of developing the effect, in this case cancer, for even the smallest doses.

These ten studies were further categorized according to the dose response model used in extrapolating the dose for a given risk. The tree for dioxin is shown in Figure 2.

DCM Tree. The tree diagram generated for DCM is more symmetrical than the dioxin tree (Figures 3 and 4). Most of the information for developing the DCM tree diagram came from Andersen and Clewell (1988). Figure 3 contains the major assumptions employed by federal agencies in determining a unit risk number. Figure 4 further defines the PBPK branch of Figure 3 by taking the mouse and human pharmacokinetic models and dividing them into several PBPK variables. According to the EPA (EPA, July 1987:73) the PBPK predictive model of Clewell and Andersen for DCM did not take into consideration several alternative ways of predicting DCM's unit risk number, such as the chemical using a different pathway to affect the body's tissues. Also the PBPK model did not allow for uncertainty of its parameter values. This tree allows those alternatives to be included in the assessment process and weighted as to their ability to predict the unit risk for DCM. Thus, by varying the parameter values, the uncertainty in which value to use can be addressed, and a much broader and more believable approach generated for determining DCM's unit risk number.

The DCM tree, Figure 3, is divided into three sections:

- 1) Dose response model, which is modeled by the LMS model. No other model has been used to obtain the unit risk number for DCM.

- 2) Species-to-human, which is broken into two subsections:

- A) Species pharmacokinetics, which was modeled traditionally using the applied dose method and only during the last couple of years has the PBPK model been considered.

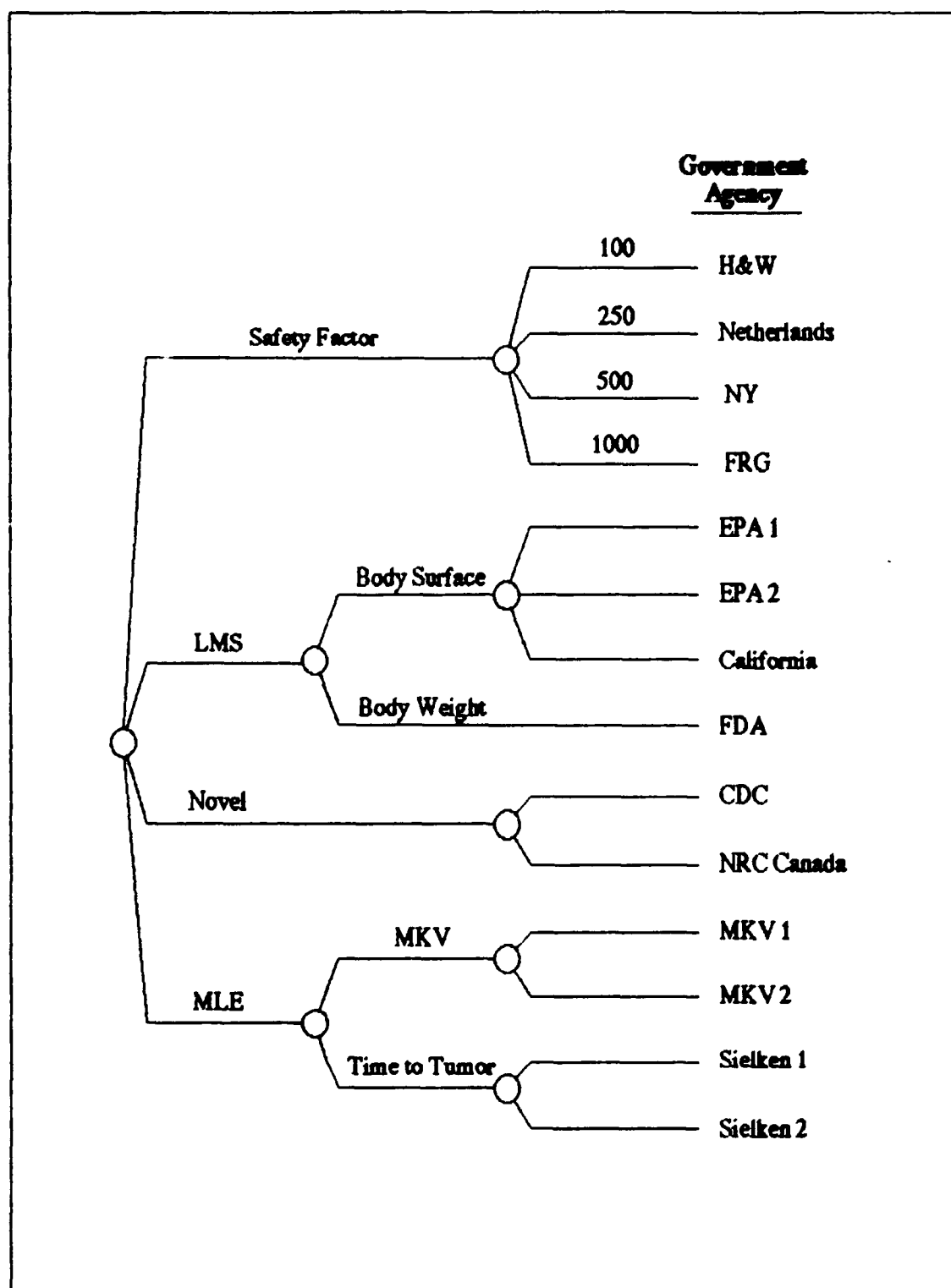


Figure 2. Dioxin Tree Diagram.

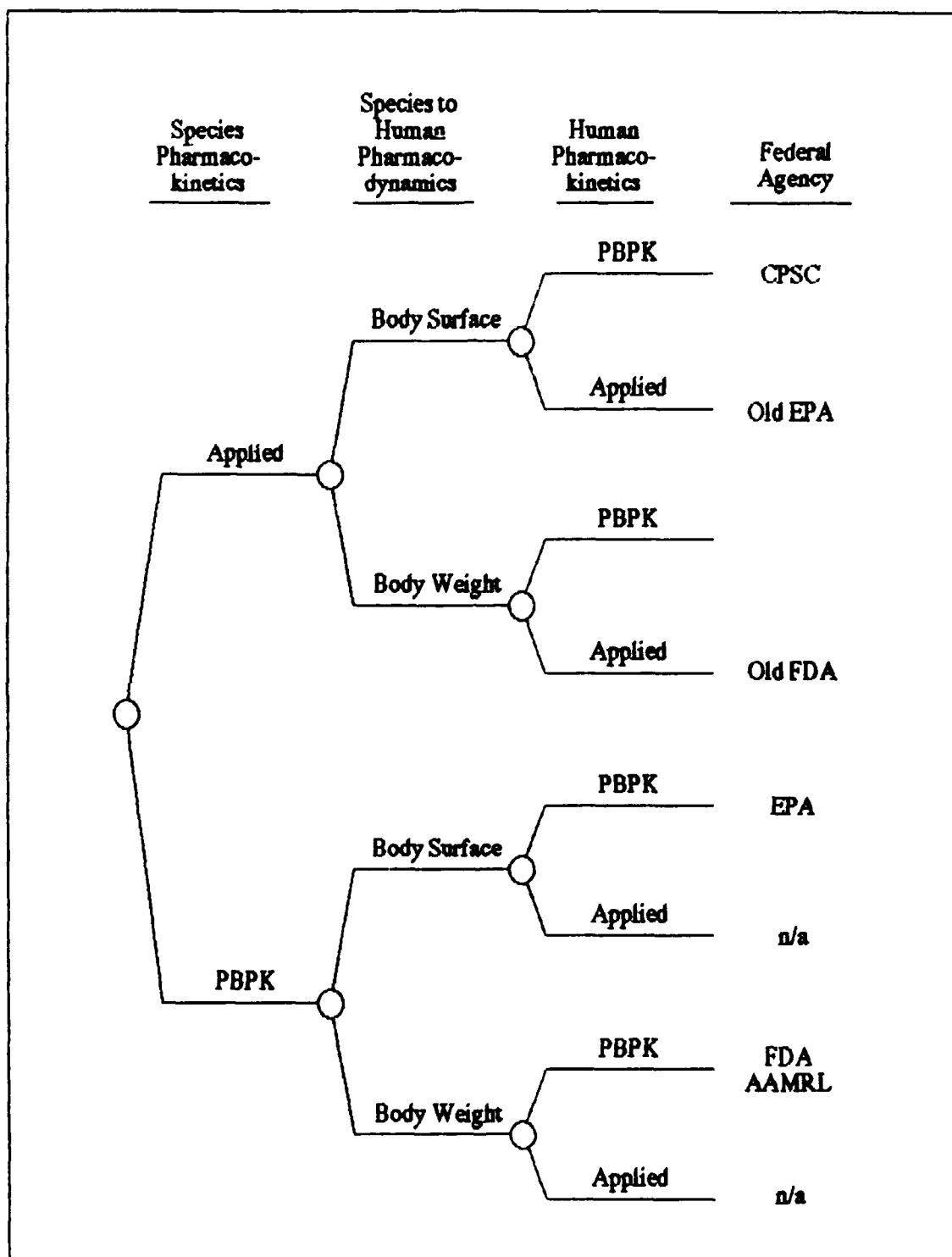


Figure 3. Methylene Chloride (DCM)
Tree Diagram.

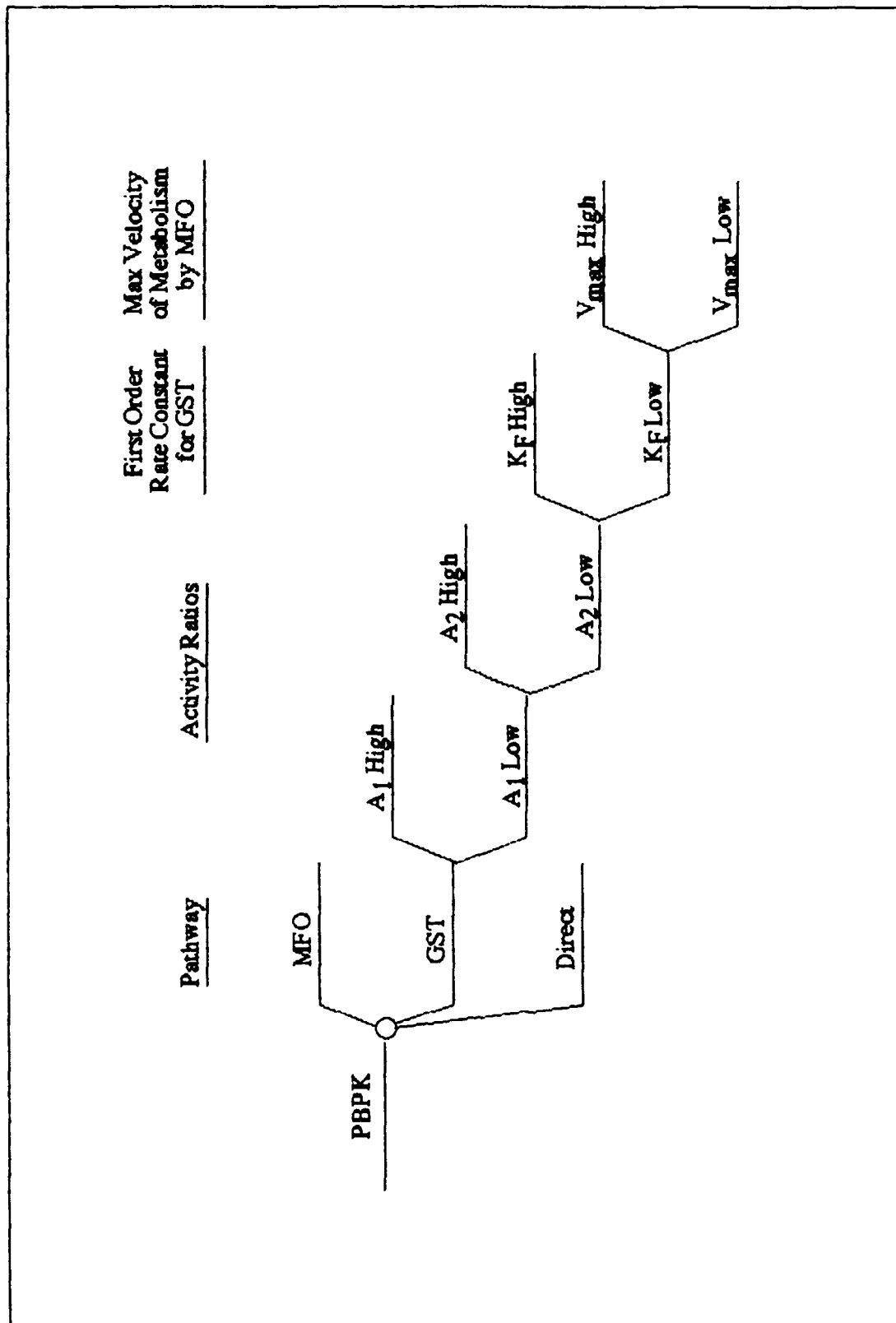


Figure 4. PBPK Variable Tree Diagram for Human & Animal

B) Pharmacodynamics, which is modeled using body surface and body weight calculations.

3) Human pharmacokinetics, which, as with section 2A above, has been traditionally modeled using the applied dose method and only during the last several years has been evaluated using the PBPK model.

DCM PBPK Tree. The PBPK portion of the DCM tree, Figure 4, is broken into two sections:

1) Pathway, the metabolism occurs via two pathways: "one dependent on oxidation by mixed function oxidases (MFO) and the other dependent on glutathione S-transferases (GST) [Andersen et al., 1987]", or DCM could act directly on the tissues of concern. Thus the tree is broken into three additional assumptions regarding the chemical mechanism responsible for causing cancer:

- A) GST pathway,
- B) MFO pathway,
- C) DCM directly.

2) Biochemical constants (metabolic constants and kinetic constants) which are further broken into:

A) A1 and A2, relative activity ratios of lung enzymes to liver enzymes in the MFO and GST pathways respectively.

B) K_f , first-order rate constant for metabolism of DCM by the GST pathway in the liver.

C) V_{max} , the maximum velocity of metabolism by the MFO pathway in the liver.

The choice of limiting the biochemical constants to the four listed above (A1, A2, K_f , V_{max}) was made by Dr. Andersen.

Assumptions. The National Toxicology Program's (NTP) inhalation bioassay (NTP, 1986) found that DCM caused cancer in male and female mice. With only one bioassay used for analysis there is no need for a bioassay branch within the DCM tree. Also there is not a branch for the dose response model node, since only the LMS dose response model has been used by federal agencies in determining DCM's unit risk number. All other PBPK values, other than A1, A2, K_f , and V_{max} , are set to

nominal values. For a discussion of these values see appendix A.

Model Summary

The various ways of obtaining the risk for dioxin and DCM have been decomposed into their different assumptions. The tree diagram allows the decision maker to focus on each assumption and assign a weight as to his belief that the assumption will aid in providing a realistic risk. The decision maker will most likely seek expert advice in determining the weights of each branch, and would most likely consult with more than one person. Combining the experts' weights into one weight for each branch poses several problems which will be discussed in the next chapter.

III. Combining Expert Opinion

The Problem

The tree diagrams developed in the previous chapter required preference weights to be assigned to the various branches. A decision maker may not know all the facts about a certain chemical and the different models, assumptions, and techniques that have been developed for predicting the unit risk. So a decision maker may seek guidance, that is, an opinion from an expert, someone who is familiar with the chemical in question, in assigning these weights. In the case of seeking only one expert's opinion about a branch's weight, as in this thesis, the expert's weighting becomes the decision maker's weight. A problem arises when the decision maker asks more than one expert for an opinion in assigning preference weights to the branches. Different experts may have different weights, and combining these weights is not a simple matter.

Combining Techniques

An expert's preference weight for each branch can be thought of as his subjective probability; so, combining a group of experts' weights is like combining subjective probabilities. There are two schools of thought for combining subjective probability (Seaver, 1976:27; Seaver, 1978:3; Edwards et al., 1979:2):

- 1) Mathematical aggregation models - which use some mathematical technique for averaging each expert's opinion.
- 2) Group behavioral techniques - which uses interaction procedures for developing a group consensus from the individuals' opinions.

Mathematical Approach. There are numerous methods for mathematically combining subjective probability, which include the arithmetic average, the geometric average, the ranked or weighted average, the bayesian and pseudo bayesian, and the personal interview. This is not all inclusive of the methods available for combining expert opinion.

Arithmetic Average. The arithmetic average is defined as the average of the different expert's weights:

$$\bar{X} = \frac{1}{N} * \text{SUM}(X_i) \text{ for } i = 1 \text{ to } N \quad (1)$$

where, X_i = the ith expert's weight

and, N = the number of experts

The arithmetic average may also take on the trimmed form where the high and low expert weights are discarded. Depending on the number of experts the two highest and lowest expert weights may be discarded. In this way the weights only include the moderate values and any extremes are eliminated. The trimmed arithmetic average is defined:

$$\bar{X}_t = \frac{1}{N-j} * \text{SUM}(X_i) \text{ for } i = 1 \text{ to } N-j \quad (2)$$

where, $j = 2$, for the one-trimmed case when the high and low value are discarded.

or, $j = 4$, for the two-trimmed case when the two highest and two lowest values are discarded.

Geometric Average. The geometric average is similar to the mathematical average, but the logarithm of the experts' weights are averaged:

$$\text{Log}(\bar{X}) = \frac{1}{N} * \text{SUM}(\text{Log}(X_i)) \text{ for } i = 1 \text{ to } N \quad (3)$$

Ranked or Weighted Average. The ranked (weighted) average is used when the decision maker does not believe each expert's weight

should be given equal treatment. The decision maker may have some reason for believing that one expert's opinion may be more credible than that of another. In this case the decision maker may rank the experts from least credible to most credible or the decision maker may ask the experts to rank themselves or one another. The ranked (weighted) average is defined as follows:

$$\bar{X}_r = \text{SUM}(W_i X_i) \text{ for } i = 1 \text{ to } N \quad (4)$$

where, $W_i = R_i / \text{SUM}(R_i)$

and, $R_i = \text{rank of the } i\text{th expert}$

Bayesian. The Bayesian approach is considered the most realistic way to combine expert subjective probabilities because a decision maker's weight for a branch is conditioned upon his prior information and upon each expert's opinion. Also, each expert's opinion is conditioned upon his prior information (Morris, 1974:1235; Hogarth, 1986:145). Quantifying these prior probabilities is extremely difficult in all but the simplest cases (Morris, 1974:1236; Hogarth, 1975:283).

Pseudo-Bayesian. Since the Bayesian approach is difficult to apply, an alternative has been proposed:

If one expert's distribution of the unknown state of nature is treated as a prior and the second expert's distribution as a likelihood, then Bayes' theorem provides a mechanism for combining them. This procedure can then be repeated successively to combine the opinions of all the experts [Chatterjee, 1987:278].

With this approach the decision maker does not have to assess each expert's prior information.

Interaction Approach. There are alternatives for combining expert opinion. These methods are not mathematically oriented, in fact they do not combine each expert's opinion, but instead use interaction

techniques so as to induce an atmosphere for free exchange of information in the hope a consensus of opinion may develop. The Delphi method is a popularly accepted method for seeking opinions from a group of experts.

Delphi Method. (Chatterjee, 1987:285-286) The Delphi method uses an iterative approach for developing a consensus of opinion. A survey is conducted where a questionnaire is distributed to the participants (experts). The experts are asked not to personally contact one another as to why they have a particular opinion. After the questions are completed the questionnaires are collected and statistically compiled and the results are made known to the participants. Who are again asked to answer the questions given the results from the first iteration, but during the second iteration the participants are asked to justify their answers. During the third iteration the participants are given each others reasons for their opinions. The questions, justification, and results are repeated a fourth time. This iterative procedure allows each participant to re-evaluate his opinion three or four times with the others participants' reasons and opinions. The Delphi method may lead to a consensus of opinion, but a consensus is not forced.

Applying the Delphi method to the tree weights would allow each expert to assign an opinion (weight) to each branch of the tree. During the first iteration the experts would only have their own prior knowledge and experience to call on. The first iteration weights would then be made available to all the experts. The experts would then be given a chance to re-evaluate their weights and to state their reasons.

The second iteration's results with reasons are made available and a third and fourth iteration may be performed. In this way each expert is permitted to update his weight given the new prior information.

On the positive side, the Delphi method (Dalkey, 1967:3):

- 1) provides anonymity and thus keeps a individual from intimidating others.
- 2) provides controlled feedback which can be used for updating the expert's opinion.
- 3) also provides a statistical group response so that each expert knows where he stands.

On the negative side, the responses and reasons generated by each expert could become less convincing with each iteration since the expert may grow tired of the procedure.

Face-to-Face. The Delphi method does not allow for personal interaction and is limited as to how thorough the feedback between experts is with each iteration. If the experts could openly confront and discuss their beliefs and understandings, then a consensus of opinion, if possible, may more easily be formed. A drawback to the face-to-face interaction is that an individual could dominate or be intimidated by others, thus forcing others to accept or reject his opinion. A consensus of opinion is ideal, but only if it is not forced. Another problem is that some people are just stubborn because they don't want to be thought of as the one who compromised. This is sometimes referred to as hardening (Chatterjee, 1987:286-287). Thus, for the sake of pride, a consensus, if possible, fails to be reached. On the positive side, by bringing together experts to openly discuss their viewpoints, a better understanding of the subject results (Matheson and Howard, 1968:39). The face-to-face method may also bring out the

critical issues. Information shared in this way may spark new ideas or a better way of understanding old thoughts.

Discussion

These techniques are just a few of the methods available for combining expert opinion and there are plenty of variations on all of them. Before recommending the best method for determining the branch weights, an overview of the forms of group opinion, the importance of conditional independence, the use of sensitivity analysis, and the choice of experts will be discussed.

Categories. (Hogarth, 1986:145) There are three classes of group opinion:

- 1) A group may want a consensus of opinion so as to make a decision within the group. This could be a husband and wife trying to decide which house to buy and they need a consensus of what they both would like to have in their home.
- 2) Another form of group opinion is the group who needs a consensus of opinion for presenting information to the public, such as in the medical field.
- 3) And finally there is the group opinion which will be used by a third person for assessing a particular problem. This is the case for the unit risk assessment tree where the third person is a decision maker who needs a weight assigned to each branch of the tree for determining the weighted average of the unit risk.

This third form of group opinion lends itself well to evaluation by the Bayesian approach for combining expert opinion. As new evidence is found for a particular chemical, the decision maker could re-evaluate the weights and calculate a new unit risk.

Conditional Independence. If independence between experts can be assumed, then the Bayesian method simplifies to just an arithmetic average. By using the face-to-face interaction approach for combining

expert opinion, the experts could then be assumed to have the same information available in assigning their estimated weights since each expert would be exposed to other experts' information. Thus, conditional independence can be assumed and the Bayesian approach is reduced to a simple expression. The Delphi method does allow for some interaction, but the amount of information transferred from one expert to another is limited. The face-to-face allows for more open communication channels between experts, and a better chance of each expert understanding the others' reasoning.

The differences of opinion left between the experts after a face-to-face debate could then be averaged into a single group opinion by either arithmetic, geometric, or ranked (weighted) averaging techniques. With the arithmetic averaging method, if the experts have a large spread between opinion values, the larger values will be favored. Since the branch weights are between zero and one, the geometric approach is not necessary. Additionally, "geometric means almost always emerge when odds ratios or densities are used" and arithmetic averaging is usually used when opinions are given in probability form (Genest and Zidek, 1986:126), as is the case here for weights. The ranked (weighted) averaging technique requires that the experts be ranked according to the decision maker's confidence in the experts ability. The decision maker may do this himself or may have the experts rank themselves. Assuming the experts to be completely familiar with the chemical being assessed, then ranking them may prove difficult and possibly embarrassing. The decision maker will most likely rank the experts as equals which reduces the ranked (weighted) equation to the arithmetic averaging technique.

Hence, the arithmetic averaging technique is the remaining choice for developing a combined group weight for the tree branches.

Sensitivity Analysis. Since it is likely that the group of experts will not come to a complete agreement as to what the weight for a particular branch must be, a decision maker should evaluate what effect this disagreement has on the outcome of the unit risk. A sensitivity analysis could be performed to assess the significance of the experts' disagreement on the consensus (Hogarth, 1975:283).

Choosing the Experts. Experts should be chosen who have both substantive and normative goodness:

"Substantive goodness refers to knowledge which the assessor [expert] has concerning the subject matter of concern. Normative goodness is the ability of the assessor to express his opinions in a probabilistic form [Hogarth, 1975:272]."

Since the choice of experts will reflect the confidence placed in the weighted average of unit risk, experts should be chosen on their understanding of the risk assessment procedure as well as their knowledge of the chemical in question. Also, each expert should have the ability to translate his preference for each assumption, to correctly estimate the unit risk number, into a weight ranging from 0 to 1.

Recommended Procedure

From the above discussion, the method for assessing the tree branch weights is as follows:

- 1) Choose a panel of experts who are familiar with the chemical being assessed and have the ability to translate their beliefs (preferences) into probabilities (weights).
- 2) Ask the experts to evaluate the tree diagram and assign weights to the individual branches.

3) The weights are then debated between experts in a face-to-face discussion so as to allow for maximum possible information exchange.

4) Any differences in weights are then averaged using the arithmetic averaging technique.

5) Finally, perform a sensitivity analysis on the tree branch weights, if a consensus has not been reached, to determine the significance of the nonconsensus.

If this procedure is followed, there will be consistency between the old assessment and a new assessment for a particular chemical when new information is uncovered. Also, there will be consistency from one chemical to another. Consistency is required to gain confidence of the constituencies who use the unit risk number of a chemical for evaluating hazardous conditions.

This recommended procedure for combining expert opinion can be used for combining the tree branch weights. In the next chapter the dioxin and DCM tree diagrams are provided to a single expert for assigning his preference and likelihood weights for each assumption in the trees. Then the trees are folded back to provide a weighted average of unit risk for DCM and a weighted average of risk-specific dose for dioxin.

IV. DCM Unit Risk Analysis

In this chapter the chemical methylene chloride (DCM) will have its unit risk number evaluated using the decomposition method. Preference weights will be assigned and a sensitivity analysis performed to determine the significant assumptions.

Assigning Preference Weights

Dr. Melvin Andersen of the Armstrong Aerospace Medical Research Laboratory was chosen as the expert for assigning preference weights to each assumption. Due to time constraints and lack of another convenient DCM expert, only one expert was consulted for assigning weights. Thus combining expert opinion as discussed in chapter 3 will not be illustrated. The two DCM tree diagrams (Figures 3 and 4) were provided to Dr. Andersen without unit risk numbers. Dr. Andersen then assigned preference weights to each branch of the tree. These weights are based on his belief of the correctness of each assumption in estimating the unit risk number. The preference weights for the DCM tree (Figure 3 only) are listed in Table 1.

According to the preference weights assigned by Andersen the pharmacodynamic assumption weights are dependent on the mouse pharmacokinetic assumptions. Also the human pharmacokinetic assumption weights (Table 1, column 3) are dependent on both the mouse pharmacokinetic and species pharmacodynamic assumptions, indicating that depending on what assumption was used for the mouse pharmacokinetics does influence the expert's (Andersen's) belief (weight) of the other

assumptions (species pharmacodynamics and human pharmacokinetics). The preference weights for the PBPK (mouse and human) portion of the DCM tree (Figure 4) are shown in Table 2. Both the mouse and human PBPK trees were assigned identical weights and so only the assumptions (variables) with their preference weights are shown.

Table 1. DCM Preference Weights given by Andersen (Andersen, 1988).

Mouse Pharmacokinetics (assumption/weight)	Species Pharmacodynamics (assumption/weight)	Human Pharmacokinetics (assumption/weight)
-> Applied/0.2 --	----> Body surface/0.3 ---	----> PBPK/0.7
	----> Body weight/0.7 ---	----> Applied/0.3
	----> Body surface/0.2 ---	----> PBPK/0.7
	----> Body weight/0.8 ---	----> Applied/0.3
-> PBPK/0.8 --	----> Body surface/0.2 ---	----> PBPK/1.0
	----> Body weight/0.8 ---	----> Applied/0.0
	----> Body surface/0.2 ---	----> PBPK/1.0
	----> Body weight/0.8 ---	----> Applied/0.0

Table 2. DCM Preference Weights for PBPK Tree (Andersen, 1988).

Pathway	Activity Ratio Lung/Liver (assumption/weight)	1st Order MFO Rate	Maximum Velocity of Metabolism by MFO
DCM/0.1	A1 high/0.5	K_f high/0.5	V_{max} high/0.5
MFO/0.2	A1 low/0.5	K_f low/0.5	V_{max} low/0.5
GST/0.7	A2 high/0.5		
	A2 low/0.5		

PBPK Variable Analysis

PBPK Variable Values. The PBPK variable values for A1, A2, K_f , and V_{max} were provided by Dr. Andersen (1988), and are shown in Table 3.

Table 3. PBPK Variables' Range (Andersen, 1988).

Species	Variable (units)	Low	Nominal	High
Mouse	A1 (ratio)	0.276	0.405	0.560
	A2 (ratio)	0.196	0.280	0.377
	K_f (1/hr)	3.000	4.000	5.000
	V_{max}^f (mg/hr)	0.900	1.054	1.200
Human	A1 (ratio)	0.000	0.001	0.004
	A2 (ratio)	0.148	0.180	0.297
	K_f (1/hr)	0.320	0.430	0.640
	V_{max}^f (mg/hr)	85.000	118.900	150.000

PBPK Sensitivity Analysis. The DCM tree as shown in Figures 3 and 4 create 6546 combinations for obtaining the unit risk number. Of the 6546 combinations of assumptions for determining the unit risk number, all but two (6544) are combinations using PBPK models. If any of the PBPK variables could be set to their nominal values (fixed) this would reduce the number of unit risk number calculations required. So a stochastic sensitivity analysis (Tatman, 1988) of the PBPK variables in Table 3 was performed in order to determine the least important variables and hopefully decrease the number of variables in the PBPK tree. The stochastic sensitivity analysis is described as follows:

The probabilistic [stochastic] sensitivity indicates how the certain equivalent [weighted average of unit risk] depends on a particular state variable [assumption] when the other state variables [assumptions] are taken with their assigned probability distributions [weights]. (von Holstein, 1983:147)

The PBPK model developed by Andersen and Clewell was used to generate the dose surrogate values for both species: mouse and human (refer to appendix A for details). The mouse dose surrogate values were used in the LMS dose response model (see appendix B), along with the NTP bioassay results for mice, to obtain the dose response values. Then these dose response values were multiplied by the human dose surrogate values (target dose) to get the unit risk numbers. Pharmacodynamic conversion (body surface) was not performed since only the sensitivity of the unit risk number to the PBPK tree variables was of interest. Any conversion would have been the same for all PBPK variables.

The mouse PBPK variables A_1 , A_2 , K_f , and V_{max} were combined with the human PBPK variables A_1 , A_2 , K_f , and V_{max} to obtain one stochastic sensitivity analysis of each PBPK variable. The range of unit risk numbers for the stochastic sensitivity analysis is shown in Figure 5 and Table 4. The stochastic sensitivity analysis shows that the PBPK variables make very little difference between their high and low values on the unit risk number as compared to the pathway assumptions. For pathway the range between the high and low unit risk numbers is significant. The unit risk range for pathway is 397 times larger than the unit risk range for variable A_1 (refer to Table 4). The unit risk number is sensitive to which pathway assumption is used (MFO or GST) and is not nearly as sensitive to the other four variables. Thus the PBPK variables A_1 , A_2 , K_f , and V_{max} were set to nominal values as listed in Table 3.

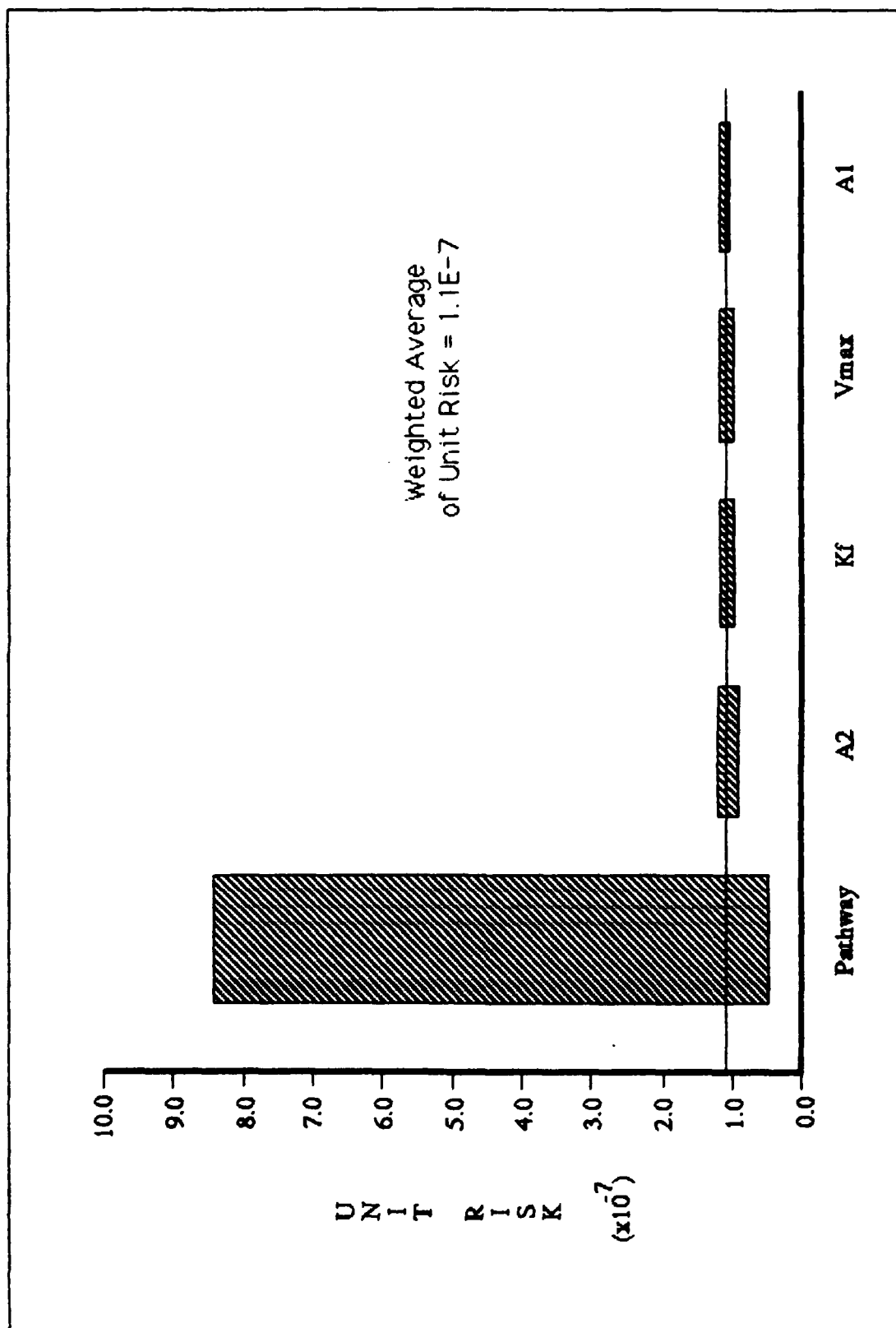


Figure 5. PBPK Stochastic Sensitivity Analysis.

Table 4. Stochastic Sensitivity of the PBPK Variables.

Variable	Lower unit risk numbers ($\times 10^{-7}$)	Upper unit risk numbers ($\times 10^{-7}$)	Difference	Ratio
Pathway	0.491	8.420	7.93	397
A2	0.982	1.230	0.248	12
K_f	1.020	1.180	0.160	8
V_{\max}	1.020	1.180	0.160	8
A1	1.090	1.110	0.020	1
weighted average of unit risk = 1.1×10^{-7} for a continuous exposure to 1 ug/m^3 of DCM				

Weighted Average of Unit Risk

With the four PBPK variables removed from the tree, it reduces to that shown in Figure 6. Now there are only 14 combinations for obtaining DCM's unit risk number. In reality there are 28 combinations because a unit risk number is calculated for both liver and lung tumors, but these are considered independent and are added together to get the unit risk number for each endpoint of the tree.

The unit risk numbers associated with each combination of assumptions in Figure 6 have been determined (refer to appendix C) and are listed in Table 5. The weighted average of unit risk is calculated by converting the unit risk numbers for each combination to logarithms and folding back the tree using the preference weights to obtain the marginal unit risk numbers, and the summation of the marginal unit risk numbers is -6.6748 , which when converted out of logarithm form gives an unit risk number of 2.1×10^{-7} .

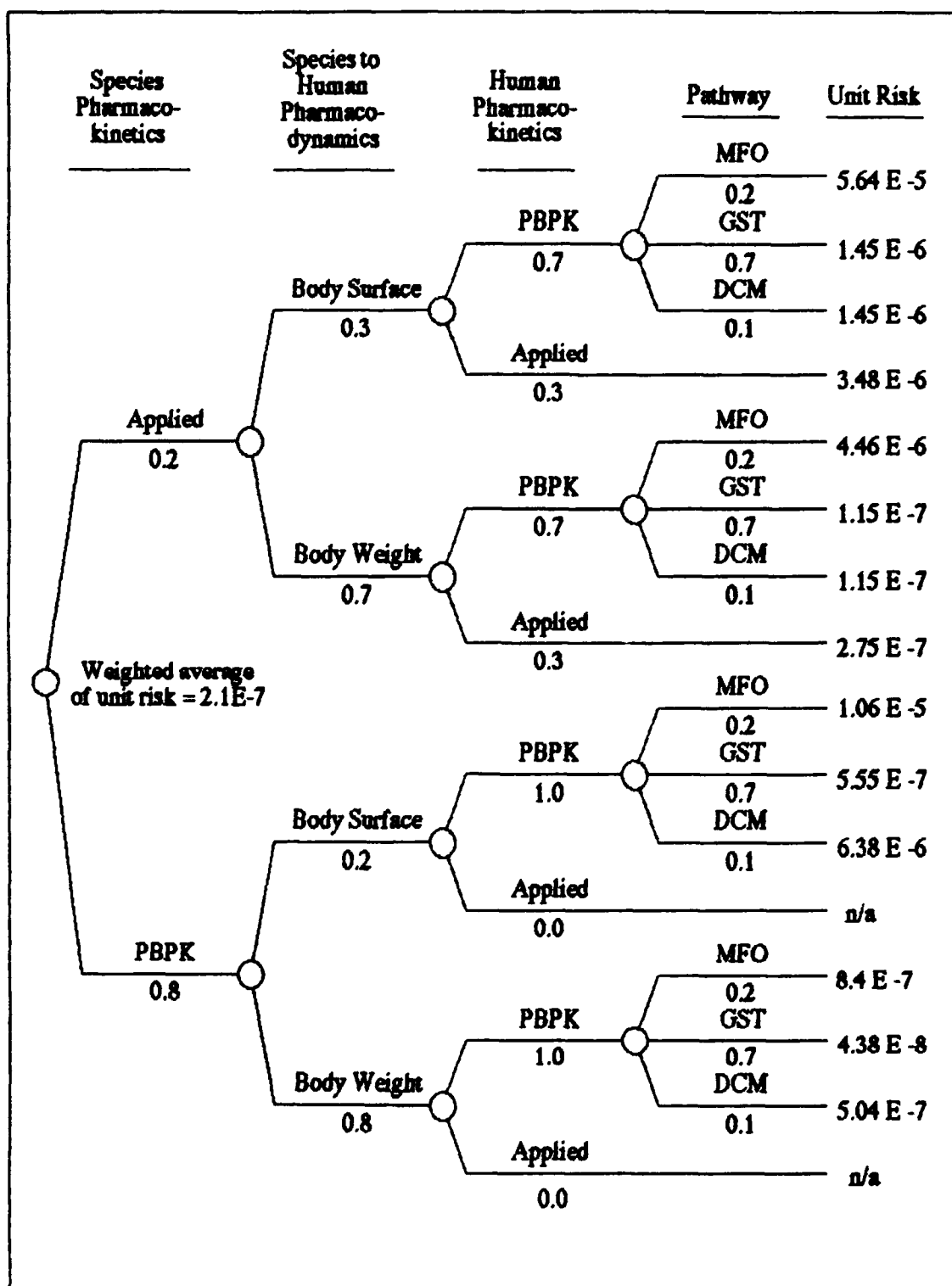


Figure 6. Reduced Methylene Chloride Tree Diagram.

Table 5. Unit Risk Numbers for the DCM Tree.

Mouse Pharmaco- kinetics	Species Pharmaco- dynamics	Human Pharmaco- kinetics	Pathway	Unit Risk Number	Log Unit Risk	Marginal Log Unit risk
applied	body surface	PBPK	MFO	5.64E-5	-4.249	-0.0357
"	"	"	GST	1.45E-6	-5.839	-0.1717
"	"	"	DCM	1.45E-6	-5.839	-0.0245
"	"	applied	n/a	3.48E-6	-5.458	-0.0983
applied	body weight	PBPK	MFO	4.46E-6	-5.351	-0.1049
"	"	"	GST	1.15E-7	-6.939	-0.4760
"	"	"	DCM	1.15E-7	-6.939	-0.0680
"	"	applied	n/a	2.75E-7	-6.561	-0.2755
PBPK	body surface	PBPK	MFO	1.06E-5	-4.975	-0.1592
"	"	"	GST	5.55E-7	-6.256	-0.7006
"	"	"	DCM	6.38E-6	-5.195	-0.0831
"	"	applied	n/a	n/a	n/a	n/a
PBPK	body weight	PBPK	MFO	8.40E-7	-6.076	-0.7777
"	"	"	GST	4.38E-8	-7.359	-3.2966
"	"	"	DCM	5.04E-7	-6.298	-0.4030
"	"	applied	n/a	n/a	n/a	n/a
					log unit risk =	-6.6748
					UNIT RISK =	2.11E-7

Using the decomposition method the unit risk number for a continuous exposure to 1 ug/m^3 of DCM is 2.1×10^{-7} . The EPA set their unit risk number to 4.7×10^{-7} for the same exposure. The decomposition method illustrated actually provides a slightly less conservative value than does the EPA's. The DCM unit risk via the decomposition method is approximately 2 times smaller than the EPA's unit risk.

Unit Risk Distribution

The unit risk distribution for DCM is shown in Figure 7. The weighted average is dominated by the weights assigned to the PBPK-body weight-GST assumption combination. Almost 45 percent of the weighted

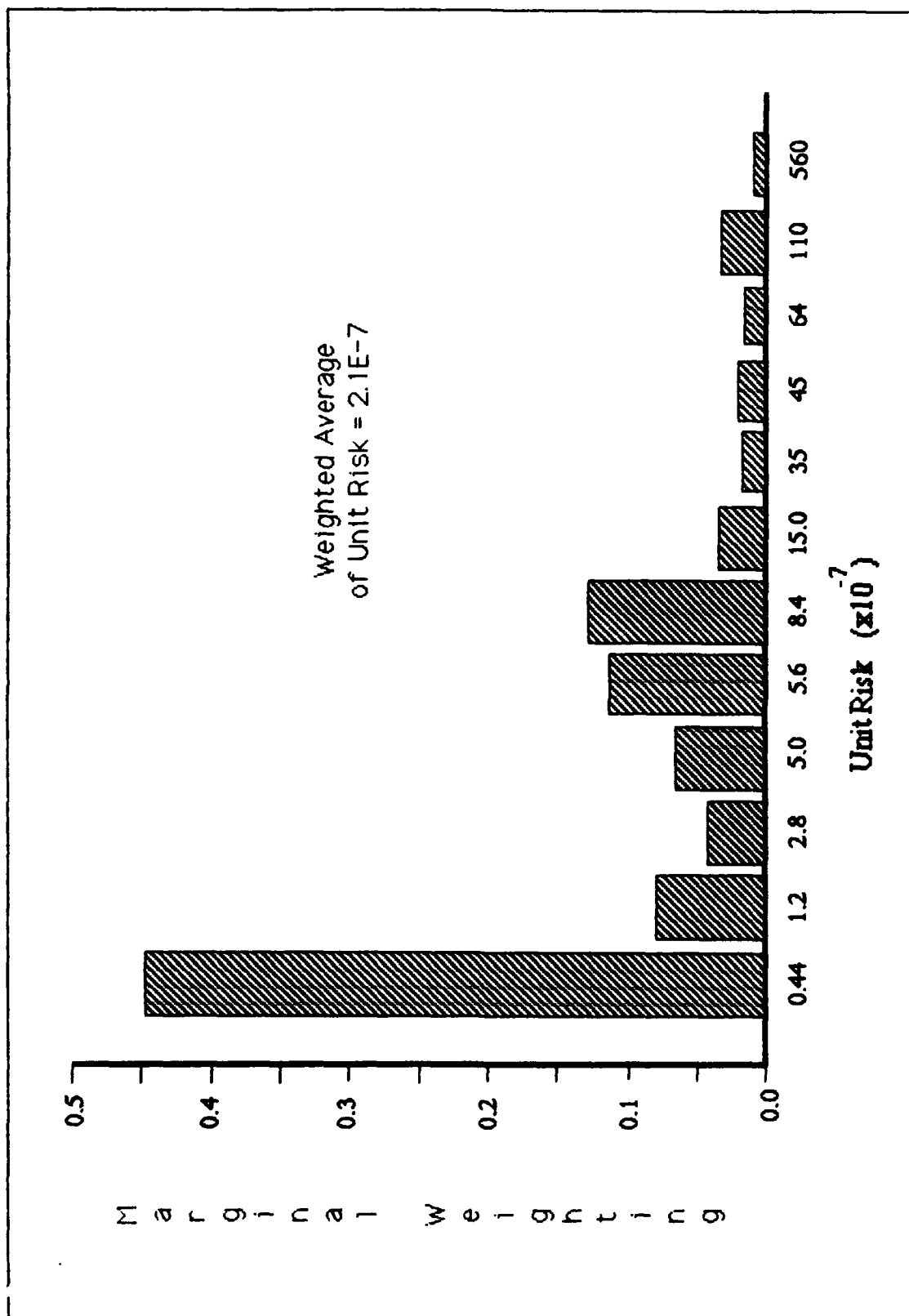


Figure 7. Unit Risk Distribution for DCM.

average is influenced by this combination. If the decision maker believes the PBPK-body weight-GST combination should not have this much influence over the weighted average, than he is free to re-evaluate the unit risk number using new preference weights. In this way the decision maker can easily analyze his unit risk number and how it was obtained.

Stochastic Sensitivity

Like the variables in the PBPK tree, the DCM tree can have a sensitivity analysis performed on its assumptions to observe how much they affect the weighted average. A stochastic sensitivity analysis was performed on the DCM tree and the results are shown in Table 6 and Figure 8.

Table 6. Stochastic Sensitivity of the DCM Tree Assumptions.

Assumption	Lower unit risk numbers	Upper unit risk numbers ($\times 10^{-6}$)	Difference	Ratio
Pathway	0.0979	1.73	1.632	4.46
Pharmaco- dynamics	0.119	1.63	1.511	4.13
Human Pharmaco- kinetics	0.198	0.589	0.391	1.07
Mouse Pharmaco- kinetics	0.168	0.533	0.366	1.00
<p>weighted average of unit risk = $2.1\text{E-}7$ for a continuous exposure to 1 ug/m^3 of DCM</p>				

Of the four assumptions, pathway still influences the weighted average more than the other three, but not as significantly as it did in

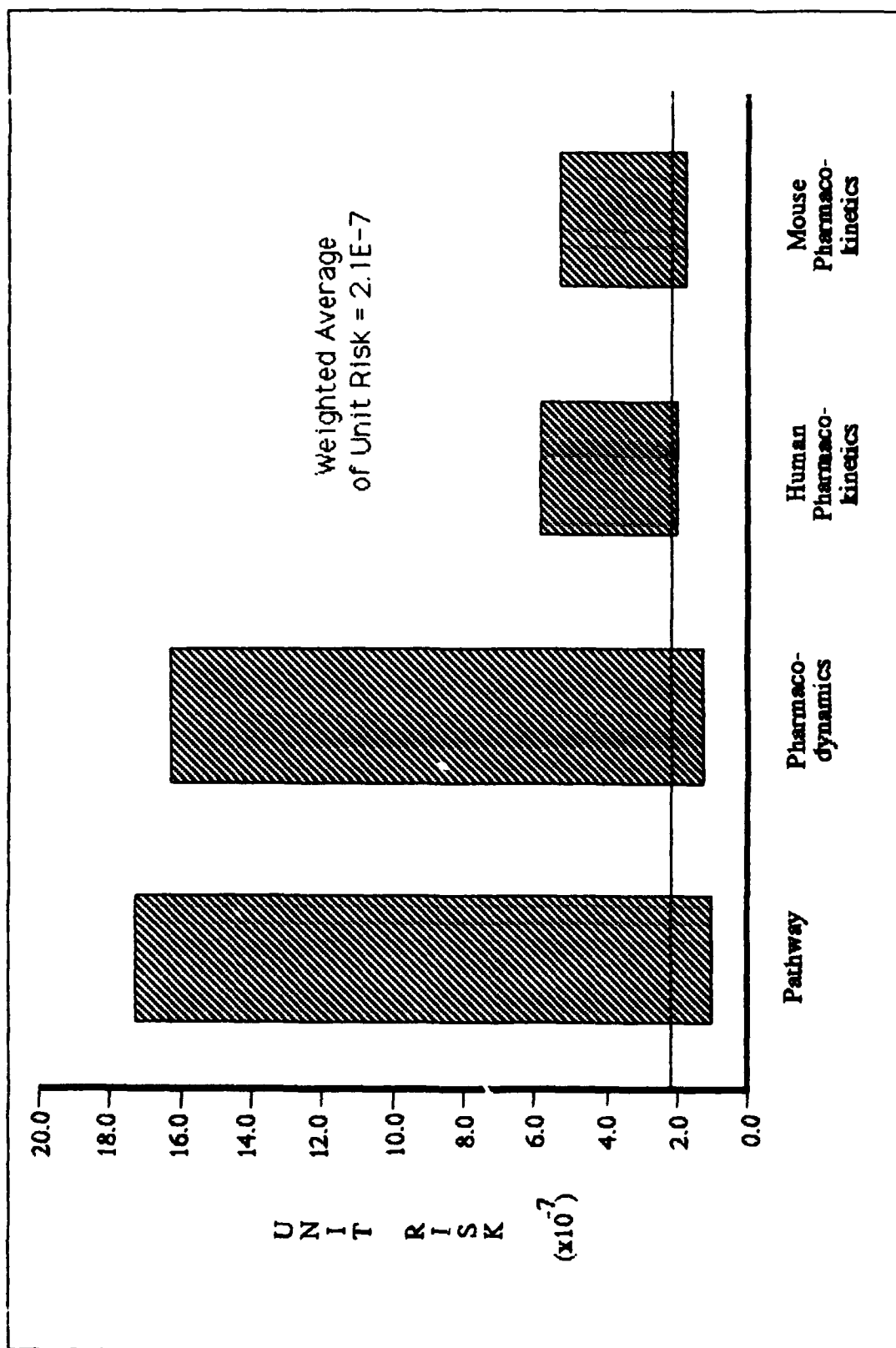


Figure 8. DCM Unit Risk Sensitivity Analysis.

the PBPK tree where it significantly dominated the four PBPK variables (4.46 times larger range as compared to 397 times larger range). Hence, the four assumptions, pathway, pharmacodynamics, human pharmacokinetics, and mouse pharmacokinetics, are important in the unit risk assessment process, at least with DCM.

Discussion

The unit risk number of DCM for a continuous exposure to 1 ug/m^3 was found to be 2.1×10^{-7} via the decomposition method. Even though the 2.1×10^{-7} seems like a good unit risk number it is not a recommendation of the Air Force, but rather an example to illustrate the decomposition method for determining the risk associated with chemicals. The significant assumptions for determining the unit risk in order of decreasing significance are: the PBPK pathway, pharmacodynamics, human pharmacokinetics, and mouse pharmacokinetics. The PBPK variables A_1 , A_2 , K_f , and V_{\max} do not make much difference. This study indicates that scientific efforts should concentrate their efforts on analyzing the significant assumptions since the uncertainty of these play a larger role in the variance of the unit risk number.

The decomposition method can be applied when evaluating the unit risk number of DCM. This method incorporates all acceptable methods for determining the unit risk of DCM whereas the EPA's unit risk is developed from only one combination of these assumptions. The decomposition method ranks each assumption as to its ability to predict the unit risk of the chemical while incorporating the most current information available to the toxicologist.

V. Dioxin Risk-Specific Dose Analysis

Dioxin is used to illustrate the flexibility of the decomposition method. Instead of calculating a weighted average of unit risk, a weighted average of risk-specific dose (RSD) will be determined for dioxin. Unlike the unit risk, which is a risk associated with a set exposure, the risk-specific dose is an exposure associated with a set risk. The dioxin tree (Figure 2) will have weights assigned to its branches and a weighted average of risk-specific dose calculated for a set risk probability of 1×10^{-6} .

Assigning Preference Weights

Again Dr. Andersen was chosen as the expert for assigning preference weights to each assumption. The dioxin tree diagram, Figure 2, was provided to Dr. Andersen; he then assigned his preference weights to each branch, which are shown in Figure 9.

Weighted Average of Risk-Specific Dose

There are 14 combinations for obtaining weighted average of risk-specific dose for dioxin (EPA, November 1987). The weighted average of risk-specific dose can now be calculated using the RSD associated with each combination of assumptions with their corresponding preference weight in Figure 9. The weighted average is calculated by converting the RSDs for each combination to logarithms and folding back the tree using the preference weights.

Using Dr. Andersen's preference weights, the decomposition method places the risk-specific dose for dioxin at 0.7 pg/kg/day. Which means

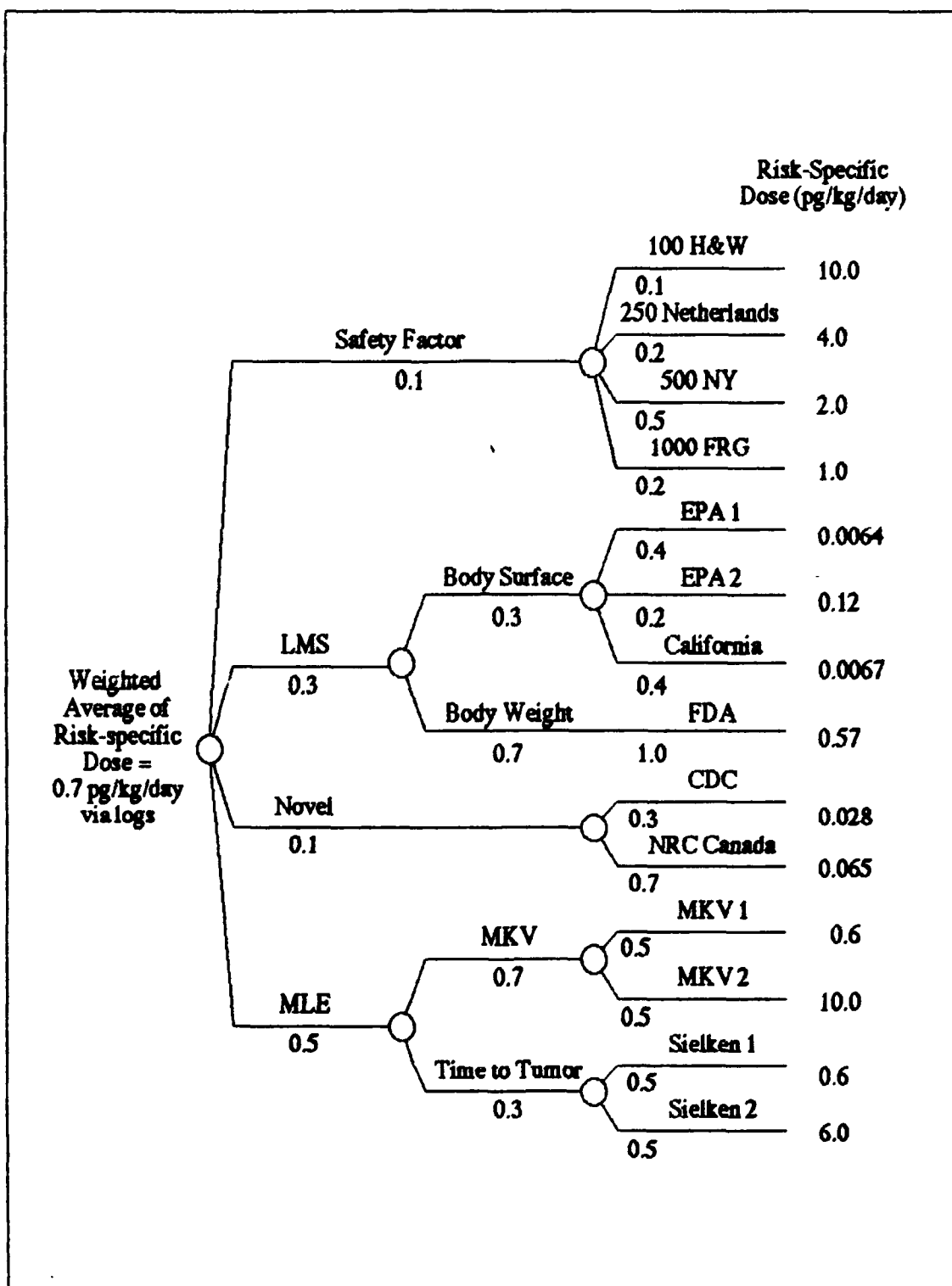


Figure 9. Dioxin Tree Diagram w/ Preference Weights.

that for a health risk of 1×10^{-6} a person may receive an internal exposure of 0.7 pg/kg/day. This converts to an external exposure dose of 2.45×10^{-6} ug/m³ using the applied dose conversion. The EPA set their risk-specific dose at 0.1 pg/kg/day for the same health risk.

Discussion

The decomposition method illustrated actually provides a slightly less conservative value than does the EPA's. The dioxin RSD via the decomposition method is approximately 7 times higher than the EPA's allowed dose. Of course different preference weights would generate a different risk-specific dose.

Again this calculated value for risk-specific dose is not a recommendation of the Air Force, but just an example to illustrate the decomposition method for determining the risk associated with chemicals. The decomposition method can be applied for evaluating the risk-specific dose of dioxin. This method incorporates all acceptable methods for determining the risk-specific dose of dioxin whereas the EPA's risk-specific dose was developed from a subjective debate of the other methods and a conservative middle ground number of 0.1 pg/kg/day was chosen. The decomposition method ranks each assumption as to its ability to predict the risk specific dose of the chemical while incorporating the most current information available to the toxicologist.

When pharmacokinetic models are developed for dioxin, the dioxin tree could easily be modified to include them. The flexibility of the decomposition method lends itself for many different risk analysis methods and allows updating as new information unfolds.

VI. Summary, Conclusions and Recommendations

Summary

There are various ways of determining the risk of a chemical. The different federal agencies responsible for setting chemical risk standards are not in complete agreement. Overestimating the risk places a financial burden on industry for maintaining the standard, and underestimating the risk puts society in jeopardy of a greater cancer threat. This study has shown how the different risk assessment methods can be decomposed into their assumptions; these assumptions are then evaluated for their ability to accurately estimate the risk of a chemical. Then the weighted assumptions are recomposed into a weighted average of risk.

Conclusions

The decomposition method can be applied to evaluating the unit risk of chemicals. This method incorporates several acceptable unit risk methods into one larger and more thorough process instead of just relying on one method, which may ignore the uncertainty associated with its assumptions. In doing so, the significance of the assumptions and variables which are used can be appraised and compared. Each assumption is weighted according to its ability of estimating the unit risk number and through this weighting an objective assessment of the chemical's risk is determined. Finally, a weighted distribution of the unit risk number can be generated for providing a better understanding of how the unit risk number was obtained and the possible range of values.

The decomposition method aids the decision maker in better understanding the chemical in question. By addressing the various assumptions used for determining the unit risk number, the decomposition method forces the decision maker to place a likely range of values and preference weights on the assumptions. In doing this the decision maker deals with the uncertainty of each assumption with the hope of obtaining a realistic and acceptable unit risk number.

Recommendations

When toxicologist develop a physiologically-based pharmacodynamic model, replacing body weight and body surface methods, then the decomposition method should be used to evaluate the significance of the new model and generate a new unit risk for DCM, or any other chemical that has had a PBPK model built for it.

The pathway the chemical (i.e., DCM) uses to attack the body should be investigated further. By reducing the uncertainty associated with the pathway, the unit risk distribution of a chemical could be greatly narrowed. The same goes for pharmacokinetics in human and laboratory animals.

The mixing of preference and likelihood weights (probabilities) needs to be addressed. The recomposition of the weighted assumptions and probability distributions of the PBPK variables into one chemical risk poses theoretical obstacles. Future research into this area of mixing weights and probabilities is required so as to provide a theoretically sound unit risk number. As for now, the decomposition method splits the tree diagram into two areas: preference weights and probabilities.

Appendix A: The Physiologically-Based Pharmacokinetic Model
for Methylene Chloride

The physiologically-based pharmacokinetic (PBPK) model for methylene chloride (DCM) was developed by Clewell and Andersen of the Armstrong Aerospace Medical Research Laboratory at Wright Patterson AFB, Ohio (Andersen et al., 1987). The parameter values used for both mouse and human are as follows:

```
MOUSED$
"MOUSE DOSE SURROGATES"$
MOUSE$
SET BW = 0.0345$
SET QCC=14.4, QPC=14.4$
SET VLC=0.04,VRC=0.05,VFC=0.04,VSC=0.78$
SET QLC=0.24,QFC=0.05,QRC=0.52,QSC=0.19$
SET PL=1.71,PF=14.5,PS=0.960,PR=1.71,PLU=1.71,PB=8.29$
SET A1=0.405, A2=0.28$
SET KF=4.0172, VMAX=1.0543, KM=0.396$
SET TITLE = "PB-PK MODEL OF MECL2"$
SET TCHNG=6,TSTOP=24,IVDOSE=0$
START$
```

```
HUMAND$
"HUMAN DOSE SURROGATES"$
HUMAN$
SET BW=70.0$
SET QCC=24, QPC = 24$
SET VLC=0.0314, VFC=0.231, VRC=0.0371, VSC=0.621$
SET QLC=0.24, QFC=0.05, QRC=0.52, QSC=0.19$
SET PB=9.7, PL=1.46, PR=1.46, PS=0.82, PF=12.4, PLU=1.46$
SET A1=0.001, A2=0.18$
SET VMAX=118.9, KM=0.58, KF=0.43$
SET TITLE = "PB-PK MODEL OF MECL2"$
SET TCHNG=6,TSTOP=24,IVDOSE=0$
START$
```

Computer output for a "MOUSED\$" is as follows:

```
D CONC,DRINK$
      CONC 4000.00000      DRINK 0.
D RISK1L,RISK1P$
      RISK1L 5474.81000      RISK1P 2369.07000
```


D RISK2L,RISK2P\$	
RISK2L 2292.31000	RISK2P 683.985000
D AUCL,AUCLU\$	
AUCL 975.769000	AUCLU 1039.83000
D CONC,DRINK\$	
CONC 2000.00000	DRINK 0.
D RISK1L,RISK1P\$	
RISK1L 5154.93000	RISK1P 2237.63000
D RISK2L,RISK2P\$	
RISK2L 1001.35000	RISK2P 313.775000
D AUCL,AUCLU\$	
AUCL 426.243000	AUCLU 477.017000

Computer output for a "HUMANDS" is as follows:

D CONC,DRINK\$	
CONC 4000.00000	DRINK 0.
D RISK1L,RISK1P\$	
RISK1L 1195.38000	RISK1P 1.21114000
D RISK2L,RISK2P\$	
RISK2L 297.479000	RISK2P 55.4503000
D AUCL,AUCLU\$	
AUCL 1010.05000	AUCLU 1045.96000
D CONC,DRINK\$	
CONC 2.8764E-04	DRINK 0.
D RISK1L,RISK1P\$	
RISK1L 8.3471E-04	RISK1P 2.1215E-06
D RISK2L,RISK2P\$	
RISK2L 3.8484E-06	RISK2P 1.7606E-06
D AUCL,AUCLU\$	
AUCL 1.3067E-05	AUCLU 3.3210E-05

The computer command file for running the DCM PBPK model (SAB.CSL) is as follows (Andersen et al., 1987):

"SAB.CMD"

"Command File for SAB.CSL - Rev. 11/18/85"
 " To Generate Data for SAB Risk Analysis "
 " Can be used for inhal if CONC > 0, or"
 " for Drinking water by setting DRINK to PPM in H2O"

PREPAR T,CA,CV,CA1,CX,RALU,ALU,CLU,AUCLU
 PREPAR RAM1P,AM1P,AM2P,CF,CL,AUCL,CS,CR
 PREPAR RAM1L,AM1L,AM2L,CV,CVF,CVL,CVS,CVR
 SET WESITG=.F.,FTSPLT=.T.

```

PROCED MOUSE
SET BW = 0.0345
SET QCC=14.4, QPC=14.4
SET VLC=0.04,VRC=0.05,VFC=0.04,VSC=0.78
SET QLC=0.24,QFC=0.05,QRC=0.52,QSC=0.19
SET PL=1.71,PF=14.5,PS=0.960,PR=1.71,PLU=1.71,PB=8.29
SET A1=0.405, A2=0.28
SET KF=4.0172, VMAX=1.0543, KM=0.396
END    $"END OF PROCED B6C3F1-MOUSE"

```

```

PROCED HUMAN
SET BW=70.0
SET QCC=24, QPC = 24
SET VLC=0.0314, VFC=0.231, VRC=0.0371, VSC=0.621
SET QLC=0.24, QFC=0.05, QRC=0.52, QSC=0.19
SET PB=9.7, PL=1.46, PR=1.46, PS=0.82, PF=12.4, PLU=1.46
SET A1=0.001, A2=0.18
SET VMAX=118.9, KM=0.58, KF=0.43
END    $"END OF PROC HUMAN"

```

```

PROCED MOUSEV    $"MOUSE VALIDATION"
MOUSE
SET TITLE = 'MOUSE -- 50 & 10 MG/KG IV'
SET CONC=0,IVDOSE=50,TSTOP=1.5,TCHNG=6.0
START
SET NRWITG=.T.,IVDOSE=10
START
PLOT CV,'LOG','LO'=.001,'HI'=100,'XHI'=1.5
SET NRWITG=.F.,IVDOSE=0
END    $"END OF PROC MOUSEV"

```

```

PROCED HUMANV    $"HUMAN VALIDATION"
HUMAN
SET TITLE = 'HUMAN -- 350 & 100 PPM INH'
SET CONC=350,TCHNG=6,TSTOP=36
START
SET CONC=100,NRWITG=.T.
START
PLOT CV,'LOG','XHI'=36,'LO'=.01,'HI'=100
SET NRWITG=.F.
END    $"END OF PROC HUMANV"

```

```

PROCED MOUSEDs    $"MOUSE DOSE SURROGATES"
MOUSE
SET TITLE = 'PB-PK MODEL OF MECL2'
SET TCHNG=6,TSTOP=24,IVDOSE=0
START
D CONC,DRINK
D RISK1L,RISK1P
D RISK2L,RISK2P
D AUCL,AUCLU
END    $"END OF PROC MOUSEDs"

```

PROCED HUMANDS '\$HUMAN DOSE SURROGATES'

HUMAN

SET TITLE = 'PB-PK MODEL OF MECL2'

SET TCHNG=6,TSTOP=24,IVDOSE=0

START

D CONC,DRINK

D RISK1L,RISK1P

D RISK2L,RISK2P

D AUCL,AUCLU

END '\$END OF PROC HUMANDS'

PROCED DS

D CONC,DRINK

D RISK1L,RISK1P

D RISK2L,RISK2P

D AUCL,AUCLU

END '\$END OF PROC DS'

PROCED MENU

..

'ENTER ONE OF THE FOLLOWING:'

..

'MOUSEV -- plot mouse validation runs'

'HUMANV -- plot human validation runs'

..

'MOUSED -- calculate mouse dose surrogates (SET CONC and
DRINK first)'

'HUMANDS -- calculate human dose surrogates (SET CONC and
DRINK first)'

'DS -- display dose surrogates'

'MENU -- type this menu'

..

END '\$END OF PROC HELP'

SET HVDPRN=.T.,GRDCPL=.F.,CJVITG=.F.

MENU

SET CMD=5

The PBPK computer model (SAB.CSL) is as follows (Andersen et al., 1987):

PROGRAM SAB.CSL - Revision = 11/18/85 at 02:21 pm

"This program will handle inhalation or drinking water Exposures"
 "To use inhalation, set the variable CONC to PPM, DRINK to 0.0"
 "To use drinking water, set DRINK to PPM in water, CONC to 0.0"
 "Default is inhalation exposure/B6C3F1 mouse/4000 PPM"
 "set CHANGE = .F. to maintain cint constant during runs"
 "Will handle iv doses if you set IVDOSE > 0.0"

INITIAL

LOGICAL	CHANGE	\$"TO CONTROL ALTERATION OF CINT DURING RUNS"
CONSTANT	TINF = 0.01	
CONSTANT	IVDOSE = 0.0	
"Constants for Mouse"		
CONSTANT	QPC=28.0	\$"Unscaled Alveolar Vent"
CONSTANT	QCC=28.0	\$"Unscaled Cardiac Output"
CONSTANT	VLC=0.04	\$"Vol Liver as % Body Wt"
CONSTANT	VFC=0.04	\$"Vol Fat as % Body Wt"
CONSTANT	VRC=0.05	\$"Vol Rapid Per. as % Body Wt"
CONSTANT	VSC=0.78	\$"Vol Slow Per. as % Body Wt"
CONSTANT	VLUC=0.0115	\$"Unscaled vol of lung tissue"
CONSTANT	QLC=0.24	\$"Flow to Liver as % Cardiac Out."
CONSTANT	QFC=0.05	\$"Flow to Fat as % Cardiac Out."
CONSTANT	QSC=0.19	\$"Flow to Slow as % Cardiac Out."
CONSTANT	QRC=0.52	\$"Flow to Rapid as % Cardiac Out."
CONSTANT	PL = 1.71	\$"Liver/Blood Part Coeff."
CONSTANT	PF = 14.5	\$"Fat/Blood Part Coeff."
CONSTANT	PS = 0.96	\$"Slow/Blood Part Coeff."
CONSTANT	PLU = 1.71	\$"Lung/Arterial Blood Part Coeff."
CONSTANT	PR = 1.71	\$"Rapid/Blood Part Coeff."
CONSTANT	PB = 8.29	\$"Blood/Air Part Coeff."
CONSTANT	CONC = 4000.0	\$"Conc. of MeCL2 in PPM"
CONSTANT	BW = 0.0345	\$"Body Wt in kg"
CONSTANT	VMAX = 1.054	\$"Unscaled VMax for Sat Pathway"
CONSTANT	KM = 0.396	\$"Km for Sat Pathway"
CONSTANT	KF = 4.017	\$"1st Order Rate Constant"
CONSTANT	A1 = 0.416	\$"VMax(Lung) / VMax(Liver)"
CONSTANT	A2 = 0.137	\$"KF(Lung) / KF(Liver)"
CONSTANT	DRINK = 0.0	\$"Concentration in PPM in H2O"
CONSTANT	CHANGE = .TRUE.	
CONSTANT	CONC2 = 0.	

"** TIMING COMMANDS"

CONSTANT TSTOP = 24.0
CONSTANT POINTS = 96.0
CONSTANT TCHNG = 6.0
 CINT = TSTOP / POINTS

"SCALED PARAMETERS"

QC = QCC*BW**0.74
QP = QPC*BW**0.74
QL = QLC*QC
QF = QFC*QC
QS = QSC*QC
QR = QRC*QC
VL = VLC*BW
VF = VFC*BW
VS = VSC*BW
VR = VRC*BW
VLU = VLUC * BW**.99

KZER = DRINK/24 * 0.102 * BW**0.7
IVR = IVDOSE * BW / TINF

END \$"END OF INITIAL"

DYNAMIC

ALGORITHM IALG = 2
T2 = T * 60.

IF (.NOT. CHANGE) GOTO NOCH
CONC3 = CONC * (1.0 - STEP(TCHNG))
IF (CONC2 .NE. CONC3) CINT = 0.0001
IF (CONC2 .EQ. CONC3) CINT = TSTOP / POINTS
CONC2 = CONC3

NOCH.. CONTINUE

DERIVATIVE

"Calculate Concentration Inhaled"
CI = 0.00348 * CONC * (1.0 - STEP(TCHNG)) \$"Conc in mg/l"

"Algebraic Solution for CA1 after gas exchange"
CA1 = (QC*CV + QP*CI) / (QC + QP/PB)
CX = CA1/PB

"Mass Balance for the Lung Tissue Compartment"

$$RALU = QC \cdot (CA1 - CA) - RAM1P - RAM2P$$

$$ALU = \text{INTEG}(RALU, 0.0)$$

$$CLU = ALU / VLU$$

$$CA = CLU / PLU$$

$$AUCLU = \text{INTEG}(CLU, 0.0)$$

$$RAM1P = A1 \cdot VMAX \cdot CA \cdot VLU / VL / (KM + CA)$$

$$AM1P = \text{INTEG}(RAM1P, 0.0)$$

$$RAM2P = A2 \cdot KF \cdot CA \cdot VLU$$

$$AM2P = \text{INTEG}(RAM2P, 0.0)$$

"AF = Amount in Fat Compartment (mg)"

$$RAF = QF \cdot (CA - CVF)$$

$$AF = \text{INTEG}(RAF, 0.)$$

$$CVF = AF / (VF \cdot PF)$$

$$CF = AF / VF$$

"AL = AMOUNT IN LIVER COMPARTMENT (MG)"

$$RAL = QL \cdot (CA - CVL) - RAM1L - RAM2L + KZER$$

$$AL = \text{INTEG}(RAL, 0.)$$

$$CVL = AL / (VL \cdot PL)$$

$$CL = AL / VL$$

$$AUCL = \text{INTEG}(CL, 0.0)$$

"AS = AMOUNT IN SLOWLY PERFUSED TISSUES (MG)"

$$RAS = QS \cdot (CA - CVS)$$

$$AS = \text{INTEG}(RAS, 0.)$$

$$CVS = AS / (VS \cdot PS)$$

$$CS = AS / VS$$

"AR = AMOUNT IN RAPIDLY PERFUSED TISSUES (MG)"

$$RAR = QR \cdot (CA - CVR)$$

$$AR = \text{INTEG}(RAR, 0.)$$

$$CVR = AR / (VR \cdot PR)$$

$$CR = AR / VR$$

"AM1L & AM2L - Amounts metabolized in LIVER"

$$RAM1L = VMAX \cdot CVL / (KM + CVL)$$

$$AM1L = \text{INTEG}(RAM1L, 0.0)$$

$$RAM2L = KF \cdot CVL \cdot VL$$

$$AM2L = \text{INTEG}(RAM2L, 0.0)$$

$$IVZONE = \text{RSW}(T.GE.TINF, 0.0, 1.0)$$

$$IV = IVZONE \cdot IVR$$

"CV = MIXED VENOUS BLOOD CONCENTRATION (MG/L)"
$$CV = (QF \cdot CVF + QL \cdot CVL + QS \cdot CVS + QR \cdot CVR + IV) / QC$$

TERMT(T.GE.TSTOP)

END \$"END OF DERIVATIVE"

END \$"END OF DYNAMIC"

TERMINAL

"RISK FACTORS AS FUNCTION OF VOLUME OF TISSUE"

RISK1L = AM1L/VL

RISK2L = AM2L/VL

RISK1P = AM1P/VLU

RISK2P = AM2P/VLU

END \$"END OF TERMINAL"

END \$"END OF PROGRAM"

Appendix B: Linear Multi-Stage Dose Response Model

The linear multi-stage (LMS) model is used by most federal agencies for calculating the dose response. The LMS model used for calculating the dose response for DCM is the GLOBAL83.FOR program provided by AAMRL and is partially discussed as follows (Howe and Crump, 1983):

To run GLOBAL83.FOR, edit the file GLOBAL83.DAT. The file looks like this:

```
Methylene Chloride Risk Assessment
3,-1,0,1,0,0,0,2
50,48,48
0,231,482
3,30,41
```

and the meaning of the lines is given below:

```
C*****
C
C   THE INPUT IS AS FOLLOWS:
CARD 1:TITLE
CARD 2:LEVELS,NDGRE,NOZERO,IADD,NAX,NAY,IBAY,LU
CARD 3:NUM(I),I=1,LEVELS
CARD 4:DOSE(I),I=1,LEVELS
CARD 5:IDEAD(I),I=1,LEVELS
C   IF NAX NOT ZERO
CARD 6:(AX(I),IAX(I)),I=1,NAX
C   IF NAY NOT ZERO
CARD 7:(AY(I),IAX(I)),I=1,NAY
C
C   ALL CARDS ARE FREE FORMAT EXCEPT TITLE
C
C LEVELS IS THE NUMBER OF DOSE VALUES
C NDCRE IS THE DEGREE OF POLYNOMIAL DESIRED
C   IF NDCRE IS NEGATIVE (MULTISTAGE OPTION) THE PROGRAM
C   AUTOMATICALLY SETS THE DEGREE TO LEVELS MINUS ONE
C NOZERO SHOULD BE ONE IF IT IS KNOWN THAT THERE IS NO BACKGROUND
C   OTHERWISE IT SHOULD BE ZERO
C IADD=1 FOR ADDITIONAL RISK**  $P(D)-P(0)$ 
C IADD=2 FOR EXTRA RISK**  $(P(D)-P(0))/(1-P(0))$ 
C NAX IS THE NUMBER OF RISKS FOR WHICH MLE DOSE AND DOSE LOWER
BOUND
C   AND/OR UPPER BOUND ARE DESIRED.
C NAY IS THE NUMBER OF DOSES FOR WHICH MLE RISK AND UPPER BOUND ON
```



```

C      RISK IS DESIRED.
C IBAY=0 IF GLOBAL 79 CONFIDENCE INTERVALS ARE ALSO DESIRED.
C IBAY=1 IF THIS OUTPUT IS NOT WANTED
C LU =0 IF LOWER BOUNDS ON DOSE ARE DESIRED
C LU =1 IF UPPER BOUNDS ON DOSE ARE DESIRED
C LU =2 FOR BOTH UPPER AND LOWER BOUNDS
C NUM(I) IS THE NUMBER OF ANIMALS ON TEST IN I-TH GROUP
C DOSE(I) IS THE DOSE VALUE FOR THE I-TH GROUP
C IDEAD(I) IS THE NUMBER OF DEFECTIVE ANIMALS AT I-TH LEVEL
C AX(I) ARE RISK AT WHICH SAFE DOSE LOWER BOUNDS ARE CALCULATED
C AY(I) ARE DOSES AT WHICH UPPER BOUNDS ON RISK ARE CALCULATED
C IAX(I) INDICATES THE SIZE OF CONFIDENCE INTERVALS.
C      IAX=1 FOR 90% ; IAX=2 FOR 95% ; IAX=3 FOR 97.5% ; IAX=4 FOR 99%
C
C*****

```

When the GLOBAL83.DAT file is ready just type @GL to run the GLOBAL83.FOR program. The output will be typed to the screen and stored in the file GLOBAL83.OUT. The unit risk can be calculated from the last entry in the output, which looks like this:

CONFIDENCE LIMITS FOR A RISK OF 0.1E-07 M.L.E. DOSE=0.2717277724E-05

UPPER CONFIDENCE LIMITS ON RISK			
90%	95%	97.5%	99%
0.120090E-07	0.126223E-07	0.131714E-07	0.138304E-07

LOWER CONFIDENCE LIMITS ON SAFE DOSE			
90%	95%	97.5%	99%
0.226271E-05	0.215275E-05	0.206302E-05	0.196471E-05

To obtain the unit risk, divide the risk, 0.1E-7, by the 95% lower confidence limit on the dose, 0.215E-5, to get 4.65E-3. If the dose used in the GLOBAL83.DAT file is a dose surrogate, as in this case, then run the PBPK model for humans at 1 ug/m³ and multiply the resulting prediction for the dose surrogate, 6.16E-6, by the risk, 0.1E-7, and divide by the 95% lower confidence limit on dose, 0.215E-5, to get a unit risk of 2.86E-8.

Appendix C: Calculating DCM Unit Risk Numbers

The 14 combinations for determining the unit risk number of DCM are shown in Figure 6. The various conversion factors used in determining the unit risk are listed below:

Human weight	= 70 kg
Human breathing rate	= 20 m ³ /day
Human exposure to 1 ppm	= 0.993314285 mg/kg/day
Mouse weight	= 0.0345 kg
Mouse rate	= 0.043 m ³ /day
Mouse exposure to 1 ppm	= 0.728261113 mg/kg/day
Body Surface conversion factor	= 12.65978455

The unit risk numbers for the 14 combinations are developed for both lung and liver tumor cases from the NTP bioassay study (1986). The unit risk numbers calculated for lung and liver are considered independent and are added together to create one unit risk number for each of the 14 combinations of assumptions from Figure 6. The methods implemented for calculating the unit risk for each combination of assumptions were outlined by Dr. Andersen and Lt. Col. Harvey Clewell of AAMRL and Dr. Murray Cohn of the Health Sciences Directorate in Washington DC. The assumption combinations are listed in the following order: mouse pharmacokinetic - species to human pharmacodynamic - human pharmacokinetic. The unit risk calculations are shown on the following pages.

Applied dose - Body weight (and Body surface) - Applied dose
combinations (Andersen and Clewell, 1988):

EFFECT	NTP BIOASSAY RESPONSE	MOUSE EXPOSURE DOSE	MOUSE INTERNAL	GLOBAL83 HUMAN INTERNAL	GLOBAL83 95% LCL at 1.00E-08
	tumor/group	ppm	mg/kg/day	mg/kg/day	risk
LUNG	3/50	0	0	0	
	30/48	2000	1457	1457	1.3272E-05
	41/48	4000	2913	2913	
LIVER	3/50	0	0	0	
	16/48	2000	1457	1457	4.8101E-05
	40/48	4000	2913	2913	
EFFECT	HUMAN EXPOSURE DOSE	HUMAN INTERNAL DOSE	TARGET DOSE	UNIT RISK 95% LCL/ Target dose	COMBINED UNIT RISK lung+liver
	ppm	mg/kg/day	mg/kg/day	risk	BODY WEIGHT
LUNG	2.88E-04	2.8571E-04	2.8571E-04	2.15E-07	2.75E-07
LIVER	2.88E-04	2.8571E-04	2.8571E-04	5.94E-08	BODY SURFACE 3.48E-06

Applied dose - Body weight (and Body surface) - PBPK method
combinations (Cohn, 1987):

PATHWAY/ EFFECT	NTP BIOASSAY RESPONSE	MOUSE EXPOSURE DOSE	MOUSE DOSE SURROGATE	DOSE SUR. MOD FACTOR	MOUSE INTERNAL
		ppm	mg/ltr/day		mg/kg/day
GST/LUNG	30/48	2000	314	1.09	1457
	41/48	4000	684	1.00	2913
GST/LIVER	16/48	2000	1001	1.14	1457
	40/48	4000	2292	1.00	2913
MFO/LUNG	30/48	2000	2238	0.53	1457
	41/48	4000	2369	1.00	2913
MFO/LIVER	16/48	2000	5155	0.53	1457
	40/48	4000	5475	1.00	2913
DCM/LUNG	30/48	2000	477	1.09	1457
	41/48	4000	1040	1.00	2913
DCM/LIVER	16/48	2000	426	1.14	1457
	40/48	4000	976	1.00	2913

PATHWAY/ EFFECT	NTP BIOASSAY RESPONSE	MOUSE EXPOSURE DOSE	GLOBAL83 HUMAN INTERNAL	GLOBAL83 95% LCL at 1.00E-08
		ppm	mg/kg/day	mg/kg/day
GST/LUNG	30/48	2000	1336	1.2753E-05
	41/48	4000	2913	
GST/LIVER	16/48	2000	1273	3.2764E-05
	40/48	4000	2913	
MFO/LUNG	30/48	2000	2751	1.9424E-05
	41/48	4000	2913	
MFO/LIVER	16/48	2000	2743	3.1728E-05
	40/48	4000	2913	
DCM/LUNG	30/48	2000	1336	1.2753E-05
	41/48	4000	2913	
DCM/LIVER	16/48	2000	1272	3.2692E-05
	40/48	4000	2913	

The modification factor is:

2000 ppm * dose surrogate at 4000 ppm

4000 ppm * dose surrogate at 2000 ppm

PATHWAY/ EFFECT	HUMAN EXPOSURE	HUMAN DOSE SURROGATE	DOSE SUR. MOD FACTOR	HUMAN INTERNAL	TARGET DOSE Int/Mod
	ppm	mg/ltr/day		mg/kg/day	mg/kg/day
GST/LUNG	2.88E-04 4000	1.7606E-06 55.45	2.26	2.8571E-04	1.2615E-04
GST/LIVER	2.88E-04 4000	3.8484E-06 297.48	5.56	2.8571E-04	5.1401E-05
MFO/LUNG	2.88E-04 4000	2.1215E-06 1.21	0.04	2.8571E-04	6.9598E-03
MFO/LIVER	2.88E-04 4000	8.3471E-04 1195.38	0.10	2.8571E-04	2.7744E-03
DCM/LUNG	2.88E-04 4000	3.3210E-05 1045.96	2.26	2.8571E-04	1.2615E-04
DCM/LIVER	2.88E-04 4000	1.3067E-05 1010.05	5.56	2.8571E-04	5.1402E-05

PATHWAY/ EFFECT	HUMAN EXPOSURE	UNIT RISK 95% LCL/ Target Dose	COMBINED UNIT RISK lung+liver
	ppm		
GST/LUNG	2.88E-04	9.89E-08	1.15E-07 BODY WEIGHT
GST/LIVER	2.88E-04	1.57E-08	1.45E-06 BODY SURFACE
MFO/LUNG	2.88E-04	3.58E-06	4.46E-06 BODY WEIGHT
MFO/LIVER	2.88E-04	8.74E-07	5.64E-05 BODY SURFACE
DCM/LUNG	2.88E-04	9.89E-08	1.15E-07 BODY WEIGHT
DCM/LIVER	2.88E-04	1.57E-08	1.45E-06 BODY SURFACE

PBPK method - Body weight (and Body surface) - PBPK method
combinations (Andersen and Clewell, 1988):

PATHWAY/ EFFECT	NTP BIOASSAY RESPONSE	MOUSE EXP. DOSE	MOUSE DOSE SURROGATE	DOSE SURROGATE MODIFIED	GLOBAL83 DOSE SURROGATE	GLOBAL83 95% LCL at 1.00E-08
		ppm	mg/ltr/dy	mg/ltr/dy	mg/ltr/dy	mg/ltr/day
GST/LUNG	30/48	2000	314	53	53	5.0456E-07
	41/48	4000	684	115	115	
GST/LIVER	16/48	2000	1001	168	168	4.3126E-06
	40/48	4000	2292	385	385	
MFO/LUNG	30/48	2000	2238	376	376	2.6538E-06
	41/48	4000	2369	398	398	
MFO/LIVER	16/48	2000	5155	866	866	1.0027E-05
	40/48	4000	5475	920	920	
DCM/LUNG	30/48	2000	477	80	80	7.6501E-07
	41/48	4000	1040	175	175	
DCM/LIVER	16/48	2000	426	72	72	1.8686E-06
	40/48	4000	976	164	164	

PATHWAY/ EFFECT	HUMAN EXPOSURE	HUMAN DOSE SURROGATE	UNIT RISK 95% LCL/ Target Dose	COMBINED UNIT RISK lung+liver
	ppm	mg/ltr/day		
GST/LUNG	2.88E-04	1.7606E-06	3.49E-08	4.38E-08 BODY WEIGHT
GST/LIVER	2.88E-04	3.8484E-06	8.92E-09	5.55E-07 BODY SURFACE
MFO/LUNG	2.88E-04	2.1215E-06	7.99E-09	8.40E-07 BODY WEIGHT
MFO/LIVER	2.88E-04	8.3471E-04	8.32E-07	1.06E-05 BODY SURFACE
DCM/LUNG	2.88E-04	3.3210E-05	4.34E-07	5.04E-07 BODY WEIGHT
DCM/LIVER	2.88E-04	1.3067E-05	6.99E-08	6.38E-06 BODY SURFACE

Bibliography

- Andersen, Melvin E. et al. "Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride," Toxicology and Applied Pharmacology, 87: 185-205 (1987).
- Andersen, Melvin E. and Lt Col Harvey J. Clewell, Chief and Deputy Chief of Toxic-Hazards Division. Personal Interviews. Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB Ohio, April 4, 20, 21, 27, May 3, 1988.
- Andersen, Melvin E., Chief of Toxic-Hazards Division. Personal Interview. Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB Ohio, Oct 4, 1988.
- Calabrese, E. J. "Animal Extrapolation: A Look Inside the Toxicologists Black Box," Environmental Science Technology, 21: 618-623 (July 1987).
- Chatterjee, Sangit. "On Combining Expert Opinions," American Journal of Mathematical and Management Sciences, 7: 271-295 (1987).
- Clewell, Lt Col Harvey J. and Melvin E. Andersen. "Risk Assessment Extrapolations and Physiological Modeling," Toxicology and Industrial Health, 1: 111-131 (1985).
- Cohn, Murray S. "Updated Risk Assessment for Methylene Chloride," (tentative title), Unpublished. Acting Division Director. Directorate for Health Sciences, Washington DC, April 24, 1987.
- Dalkey, Norman C. Delphi, Santa Monica CA: The RAND Corporation, October 1967 (AD-660554).
- Edwards, Ward et al. Research on the Technology of Inference and Decision, Oct 1977 - Dec 1978. Contract N00014-76-C0074. Los Angeles: Social Science Research Institute University of Southern California, January 1979 (AD-A073369).
- , Environmental Protection Agency. "Guidelines for Carcinogen Risk Assessment," Federal Register, 51: 33994-34003, September 24, 1986 (FR Doc. 86-19601).
- , Environmental Protection Agency. "Update to the Health Assessment Document and Addendum for Dichloromethane (Methylene Chloride): Pharmacokinetics, Mechanism of Action, and Epidemiology," EPA/600/8-87/030A, July 1987.
- , Environmental Protection Agency. "A Cancer Risk-Specific Dose Estimate," EPA-600, November 1987.

- Genest, Christian and James V. Zidek. "Combining Probability Distributions: A Critique and an Annotated Bibliography," Statistical Science, 1: 114-148 (Jan-Feb 1986).
- Hogarth, R.M. "Cognitive Processes and the Assessment of subjective Probability Distributions," Journal of the American Statistical Association, 70: 271-294 (June 1975).
- Hogarth, R.M. Comment to "Combining Probability Distributions: A Critique and an Annotated Bibliography," Statistical Science, 1: 145-146 (Jan-Feb 1986).
- von Holstein, Carl-Axel S. Stael. "A Tutorial in Decision Analysis," The Principles and Applications of Decision Analysis, Volume I, General Collection, edited by Howard and Matheson. Berkley CA: Strategic Decisions Group, 1983.
- Howe, Richard B. and Kenny S. Crump. "GLOBAL83 - Linear Multistage Dose Response Model," Computer Program. Ruston LA: Science Research Systems, Inc., 1983.
- Matheson, J.E. and R.A. Howard. "An Introduction to Decision Analysis," The Principles and Applications of Decision Analysis, Volume I, General Collection, edited by Howard and Matheson. Berkley CA: Strategic Decisions Group, 1983.
- Menzel, Daniel B. "Physiological Pharmacokinetic Modeling," Environmental Science Technology, 21: 944-950 (October 1987).
- Morris, Peter A. "Decision Analysis Expert Use," Management Science, 20: 1233-1241 (May 1974).
- Munro, J.C. and D.R. Krewski. "Risk Assessment and Regulatory Decision Making," Fd Cosmet Toxicology, 19: 549-560 (1981).
- , National Toxicology Program. "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dichloromethane in F344/N Rats and B6C3F1 Mice (inhalation studies)," U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, January 1986 (NIH publication no. 86-2562, NTP TR 306)
- , Office of Science and Technology Policy. "Chemical Carcinogens; A Review of the Science and Its Associated Principles," Federal Register: 10371-10442, March 14, 1985 (FR Doc. 85-5981).
- Seaver, David A. Assessment of Group Preferences and Group Uncertainty for Decision Making, Jul 1975 - Sep 1976. Contract N00014-76-C0074. Los Angeles: Social Science Research Institute University of Southern California, June 1976 (AD-A033246).

Seaver, David A. Assessing Probability with Multiple Individuals: Group Interaction versus Mathematical Aggregation, Nov 1977 - Dec 1978. Contract N00014-76-C0074. Los Angeles: Social Science Research Institute University of Southern California, December 1978 (AD-A073363).

Shabecoff, Philip. "E.P.A. Reassesses the Cancer Risks of many Chemicals," The New York Times, 137;A-1,A-17 (January 4, 1988).

Tatman, Capt Joseph A. "Stochastic Sensitivity," Class handout distributed in Math 570, Decision Analysis. School of Engineering, Air Force Institute of Technology (AU), Wright Patterson AFB OH, Feb 1988.

Wilkinson, Chris F. "Being More Realistic About Chemical Carcinogens," Environmental Science Technology, 21: 843-847 (September 1987).

VITA

Captain David S. Clement [REDACTED]

[REDACTED] In 1977 [REDACTED]

attended Virginia Polytechnic Institute and State University (VPI), from which he received the degree of Bachelor of Science in Mechanical Engineering. While at VPI he spent 3 years as a coop student working at Babcock and Wilcox' Naval Nuclear Fuel Division in Lynchburg, Virginia. He joined the Air Force through the College Senior Engineering Program (CSEP). After graduating from VPI in August 1982 he received his commission in the USAF through the OTS program. He was then assigned to the 6595th Shuttle Test Group at Vandenberg AFB, California as a facility manager of the shuttle launch complex (SLC6). He is currently working on a M.S. of Operations Research at the Air Force Institute of Technology at Wright Patterson AFB, Ohio. Upon graduating from AFIT in December 1988 he will be assigned to the Defense Logistics Agency Operations Research Office at the Defense General Supply Center in Richmond, Virginia.

[REDACTED]

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT SECURITY CLASSIFICATION Classified			1b. RESTRICTIVE MARKINGS		
2a. SECURITY CLASSIFICATION AUTHORITY			3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for Public Release; distribution unlimited		
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE					
4. PERFORMING ORGANIZATION REPORT NUMBER(S) AFIT/GOR/MA/88D-2			5. MONITORING ORGANIZATION REPORT NUMBER(S)		
6a. NAME OF PERFORMING ORGANIZATION School of Engineering		6b. OFFICE SYMBOL (If applicable) AFIT/ENS		7a. NAME OF MONITORING ORGANIZATION	
6c. ADDRESS (City, State, and ZIP Code) Air Force Institute of Technology (AU) Wright-Patterson AFB, Ohio 45433-6583				7b. ADDRESS (City, State, and ZIP Code)	
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Aerospace Medical Research Lab		8b. OFFICE SYMBOL (If applicable) AAMRL/TH		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code) Wright-Patterson AFB, Ohio 45433				10. SOURCE OF FUNDING NUMBERS	
		PROGRAM ELEMENT NO.		PROJECT NO.	TASK NO.
				WORK UNIT ACCESSION NO.	
11. TITLE (Include Security Classification) DEALING WITH UNCERTAINTY IN CHEMICAL RISK ANALYSIS					
12. PERSONAL AUTHOR(S) ement, David Sutherland, B.S., Capt, USAF					
13a. TYPE OF REPORT MS Thesis		13b. TIME COVERED FROM _____ TO _____		14. DATE OF REPORT (Year, Month, Day) 1988 December	
15. PAGE COUNT 75					
16. SUPPLEMENTARY NOTATION Keywords					
17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP	Toxicology, Toxic Hazards, Tree Diagrams, Uncertainty, Chemical Risk, Combining Subjective Probabilities, Carcinogens, Methylene Chloride, Dioxin, Unit Risk, These		
06	11				
12	03				
19. ABSTRACT (Continue on reverse if necessary and identify by block number) See attached for ABSTRACT Thesis Chairman: Joseph A. Tatman, Captain, USAF Strategic Decision Program, AFIT/MA Air Force Institute of Technology (AU) Wright-Patterson AFB, Ohio 45433 <i>(AW) ✓</i> <i>Approved</i> <i>12 Jan 1989</i>					
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS			21. ABSTRACT SECURITY CLASSIFICATION Unclassified		
22a. NAME OF RESPONSIBLE INDIVIDUAL Joseph A. Tatman, Capt, USAF			22b. TELEPHONE (Include Area Code) (513) 255-3098		22c. OFFICE SYMBOL AFIT/MA

UNCLASSIFIED

ABSTRACT

↙
For a given chemical there are usually several methods for estimating the risk. Each method is based on different assumptions. The arguments are plentiful for each method, but which method best estimates the risk? Choosing one method over another could lead to faulty risk estimates, thus the traditional methods have been very conservative to avoid underestimating the risk. With advances made in pharmacokinetics the EPA as come under pressure to re-evaluate its procedure for assigning risk. Which method or methods should be used and how much emphasis should be placed on each one? This study decomposes the various methods into their corresponding assumptions. A tree diagram is generated to describe the combinations of assumptions that make up each unit risk method. A subjective weight is assigned to each assumption (branch of the tree) to characterize its validity in estimating the risk. From this a weighted average of risk is calculated. A procedure is recommended for combining expert opinion when several experts are utilized in assigning the subjective weights. Two examples involving Methylene Chloride and 2,3,7,8-tetrachlorodibenzo-p-dioxin illustrate the decomposition method of estimating chemical risk.

Keywords;

See 100-100-10

UNCLASSIFIED

C